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ORGANIC SEMINAR ABSTRACTS

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Fall Semester, 1982

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DOUBLE BRIDGEHEAD OLEFINS IN THE BICYCLO[4.3.1]DECADIENE SYSTEM

Reported by William Boulanger Sept. 2, 1982

The concept that small-ring bridgehead olefins represents a class of strained and consequently higher-energy compounds was first put forward by J. Bredt[1] in 1924, resulting in what is now called "Bredt's Rule"[2]. Although Bredt's Rule was originally restricted to pinanes, camphanes, and related systems, it has been generalized more recently by Wiseman[3].

Several reviews have appeared over the years, each making an attempt to define the relative stability of a particular bridgehead olefin based on various criteria. Fawcett[2] proposed a relationship of stability to the total number of bridging atoms, an approach which found only superficial success. A later review by Köbrich[4] introduced many empirical rules too awkward to apply in practice.

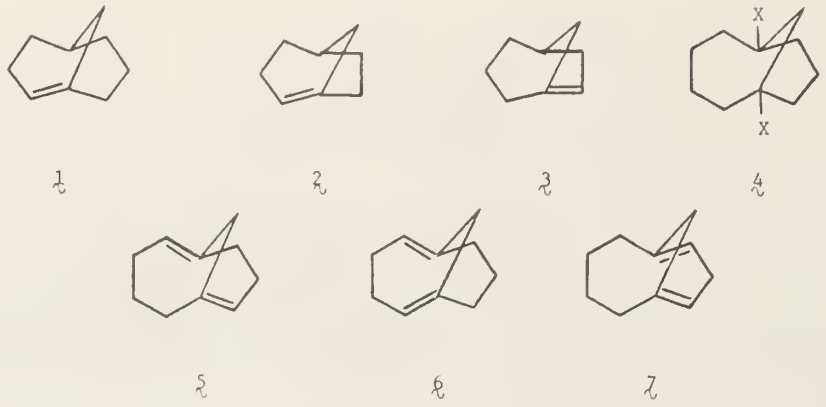
Modern computer technology has at last allowed a more fundamental approach to prediction of relative stabilities of bridgehead olefins, and the success has been reviewed recently by Maier and Schleyer[8]. Using force-field calculations, Burkert[5] and Ermer[6] determined non-planar deformation energies which correlated to experimental data of a restricted number of olefins. Lesko and Turner[7] pointed out the need to consider the strain energy of a bridgehead double bond as a composite of the extra strain associated with the double bond and the residual energy associated with the carbon skeleton. Maier and Schleyer[8] used this concept to calculate, with good experimental agreement, not only the relative stabilities of the known bridgehead olefins, but also a working guide as to which are isolable, observable, or unstable. Their paper represents the state of the art.

Of the now-surpassed empirical rules, only the observation of Wiseman[3] remains untouched; that the relative stabilities of bridgehead olefins correlates to the relative stabilities of the cyclo-olefins in which the double bond is both endocyclic and transoid. So, where trans-cyclooctene[9] is isolable, and trans-cycloheptene is not[10], 1 was easily prepared[11,12] while 2 and 3[13] (containing the trans-cycloheptene) were stable only at -30°.

The incorporation of not one, but two double bonds in a bridge-ring system is a natural outgrowth of the previous work. These compounds include cycloheptatrienes[14], bridged aromatic systems[15] and compounds with bent, not twisted, double bonds[16]. A few stable compounds of the twisted diene class have been prepared[17,18,19], and at least one proposed as an intermediate[20].

We were interested in preparing and studying the thermal reactions of the more stable bridgehead dienes in the bicyclo[4.3.1.]decadiene system, which represented compounds of borderline stability at the initiation of the work (1975). Two compounds incorporating this system[17,18] have since appeared in the literature.

Our initial approach was the elimination of two HX from 4, for which access is known[21]. In the case where X = OAc pyrolysis produced rearrangement products which deuteration studies suggest originated from 5, 6, and 7. By independent preparation of a pyrolysis intermediate, 6 was prepared as a stable compound.



1 2 3 4

5 6 7

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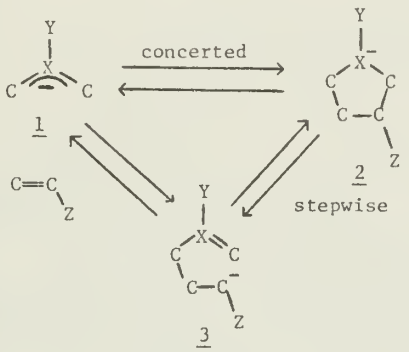
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1,3-ANIONIC CYCLOADDITIONS[1]

Reported by Kenneth D. Wilson September 23, 1982

The symmetry allowed [$\pi^4+\pi^2$] cycloadditions of dienes [4+2] and 1,3-dipoles [3+2] with olefins are well known reactions important both mechanistically and synthetically.[2,3] In contrast the analogous [3+2] cycloaddition reactions of allyl and azallyl anions with olefins remain rather obscure and of limited synthetic value.[1,4] This seminar will examine the scope, mechanism and limitations of the 1,3-anionic cycloaddition reaction and will describe the use of 2-amidoallyl anions to extend the scope of this cyclization.

The 1,3-anionic cylcoaddition of allyl anion 1a with an olefin to form cyclopentyl anion 2a is an energetically unfavorable process except with highly reactive olefins such as benzyne.[5,8b] Cyclized products are obtain-



a X=C, Y=H
b X=C, Y=Ph
c X=C, Y=CN
d X=C, Y=CON^{i}Pr$_2$
e X,Y=N

Z=aryl, vinyl, CON^{i}Pr$_2$, SPh, SiPh$_3$, SePh, Ph$_2$, AsPh$_2$

able from allyl anions 1b-d which have anion stabilizing substituents at the 2-position and from 2-azaallyl anions.[6,7,8] In these cases the substituent or nitrogen atom stabilizes the resulting cyclopentyl anion 2b-e. The reaction is also limited to cycloadditions with olefins and acetylenes having anion stabilizing substituents and to azobenzene, arylimines, arylnitriles, isonitriles and carbon disulfide.[6,7,8,9]

The regiospecificity observed for the cycloaddition of unsymmetrical olefins[7c,i,j,l,m] and the trapping of acyclic products at low temperatures[6d,h,7g,o,q,r,11] suggest a stepwise addition-cyclization mechanism (1→3→2).[1,5] Examples in which the olefin geometry is maintained during the cycloaddition are also known.[6c,d,g,7d,h]

One of the major limitations to extending the 1,3-anionic cycloaddition reaction has been the problem of generating suitable allyl anions in high yield. Recent work has shown that β' metalation of methacrylamides provides a convenient source of allyl anions and that these anions undergo 1,3-anionic cycloaddition.[10,11,12]

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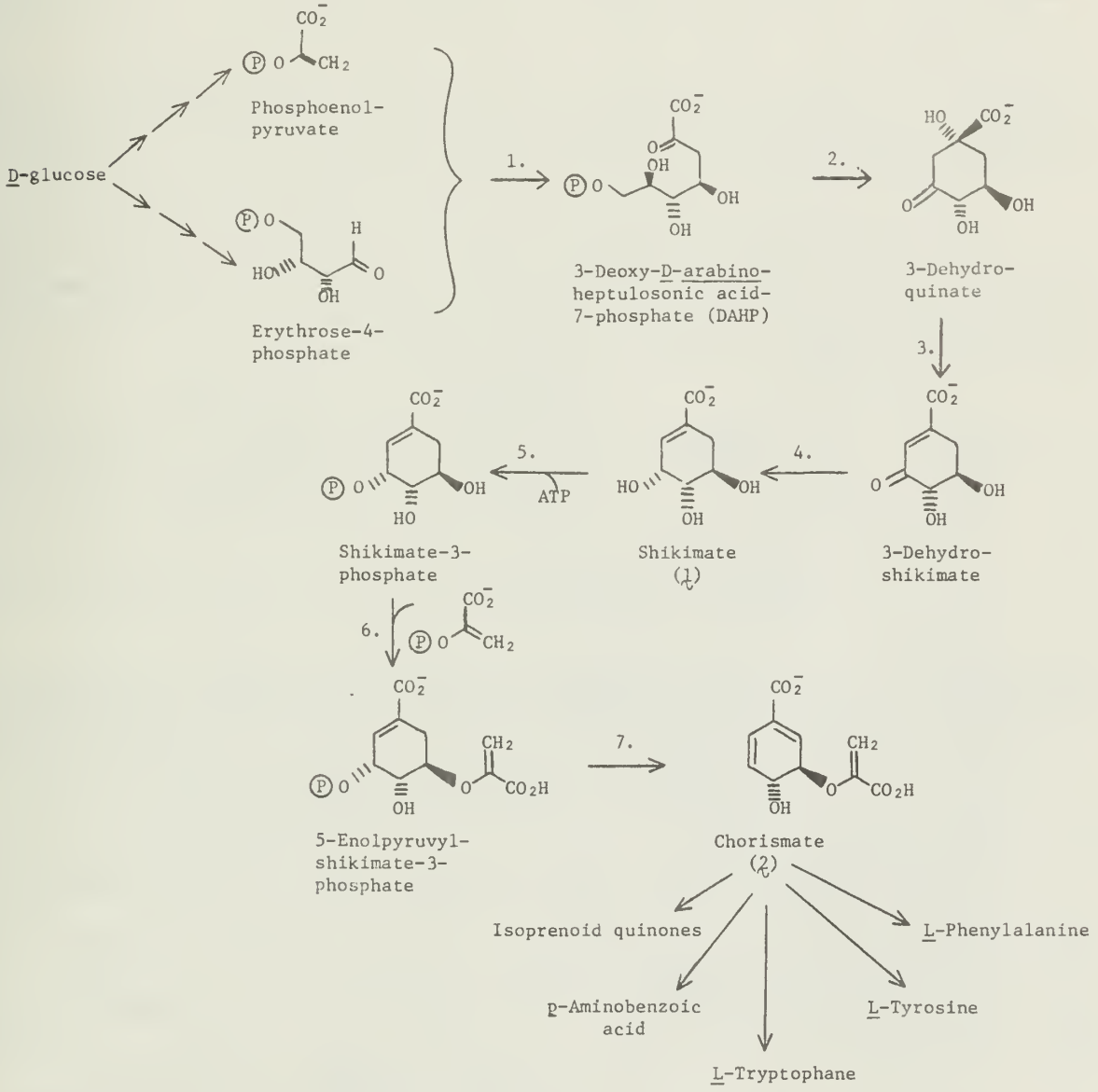
THE ROLE OF THE SHIKIMATE PATHWAY IN THE BIOSYNTHESES OF C_7N ANTIBIOTICS

Reported by Marietjie Potgieter October 7, 1982

(-)-Shikimic Acid (1) was first described by Eykmann in 1885[1] as a natural product from the plant Illicium religiosum Sieb., and it was from the Japanese name of this plant, shikimi-no-ki, that the name shikimic acid was derived. Among the few general biosynthetic routes to natural products, the shikimic acid pathway produces some of the most structurally diverse, biochemically important primary and secondary metabolites found in nature, eg. aromatic aminoacids, vitamins, coenzymes, antibiotics, mycotoxins and alkaloids.

The main stem of the pathway leads to the formation of chorismic acid (2) which is the common intermediate for most of the branches of the pathway (Scheme I).[2-5] The building blocks of shikimic acid are phosphoenolpyruvate and erythrose-4-phosphate which combine to give the seven-carbon sugar 3-deoxy-D-arabino-heptulosonic acid-7-phosphate (DAHP).

Scheme I



1. DAHP synthetase, 2. 3-Dehydroquinate synthetase, 3. 3-Dehydroquinate dehydratase, 4. 3-Dehydroshikimate reductase, 5. Shikimate kinase, 6. 5-Enolpyruvylshikimate-3-phosphate synthetase, and 7. Chorismate synthetase.

Cyclization leads to the first carbocyclic compound, 3-dehydroquinate, which is dehydrated to give 3-dehydroshikimate, and reduced to form shikimate (1). Phosphorylation in the 3-position is followed by the addition of another molecule of phosphoenolpyruvate. Subsequent 1,4-elimination of the elements of phosphoric acid leads to the formation of chorismate (2) from which five different biosynthetic routes diverge to form essential aromatic metabolites. The elucidation of the steps in the common pathway was accomplished by the combined use of auxotrophic (nutritionally dependent) mutants, isotopically labeled precursors and enzymic studies. The enzymes involved as catalysts in each of the steps were subsequently isolated from bacterial mutants and characterized.[2-5]

It was recently found that the m-C-C_6-N or C_7N units present in a large number of antibiotics isolated from micro-organisms, are derived from glucose in a shikimate-related pathway.[6] This C_7N structural unit consists of a six-membered carbocyclic ring with an exocyclic carbon and a nitrogen substituent meta to each other. The first approach to determine the origin of the carbons of the C_7N unit of rifamycin[7] was based on a comparison of the incorporation patterns of [1-^{13}C]glucose and [1-^{13}C]-glycerate with the distribution of label in shikimic acid when it was biosynthesized from [1-^{14}C]glucose.[5] For more reliable results, Hornemann and coworkers[8] administered [3-^{14}C]pyruvic acid and [4-^{14}C]erythrose, respectively, to a growing culture that produced mitomycin C and determined the labeling of the C_7N unit of the antibiotic by a series of degradations. [U-^{13}C]glucose[9] was used in this laboratory as an in situ source of [U-^{13}C]-phosphoenolpyruvate and [U-^{13}C]erythrose-4-phosphate and their modes of incorporation into the C_7N units of pactamycin[10], geldanamycin[11], and validamycin[6] were determined by ^{13}C NMR spectroscopy including ^{13}C homonuclear decoupling experiments.

The determination of the point at which the biosyntheses of C_7N units diverge from the shikimate pathway is still inconclusive. Swiss workers[12] have determined that the branch point for rifamycin lies between DAHP and shikimic acid, but no significant incorporation of any of the ^{14}C-labeled intermediates under consideration have been achieved.

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CHIRAL CROWN ETHERS AND THEIR USE IN ENANTIOSELECTIVE HOST-GUEST COMPLEXES WITH CHIRAL AMINES AND AMMONIUM SALTS

Reported by Karl Neidert October 14, 1982

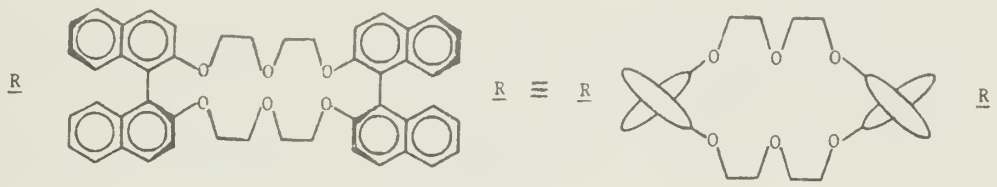
This report will examine the basis of the high enantiomer selectivity by chiral heterocycles for chiral amines and ammonium salts. The report will also examine asymmetric reactions involving chiral heterocycles with prochiral reactants.

Cyclodextrans have been proposed as enzyme models, as well as host-guest complexes, and cyclodextrans do show enantiomeric selectivity. However because they have been recently reviewed[1,2] they will not be discussed.

Cram has defined the host, of a host guest complex, as an organic molecule or ion whose binding sites converge. The guest has been defined as a molecule or ion whose binding sites diverge.[3,4] Lehn has suggested that the term cryptand be used to describe all types of cavity-containing ligands and the term cryptate to refer to a complex between a cryptand and another molecule.

Chiral crown ethers have been synthesized with the chiral element being: 2,2'-dihydroxy-1,1'-binaphthyl[3,7], modified L-tartaric acid[6,8,9,10], modified D-mannitol[6,11,12,13], modified L-threitol[12], modified D-glucose[14], modified D-galactose[14], and 2,2'-dihydroxy-9,9'-spirobifluorene.[15]

One of the most successful approaches, to chiral recognition with host-guest involves use of a chiral component derived from 2,2'-dihydroxy-1,1'-binaphthyl. The binaphthyl is used to form crown ethers of the structure D(OEOEO)$_2$D (1) where D is the chiral 1,1' binaphthyl group substituted in the 2,2' position with oxygen (O) attached to ethylene groups (E) to form a macrocyclic ring.



1 [D(OEOEO)$_2$D]

These chiral hosts, when substituted at the 3 and 3' postitions on one binaphthyl ring with methyl groups, have been shown to selectively complex one enantiomer of phenylglycine methyl ester ammonium hexafluorophosphate salt by a factor of 30.[16] The system with only one chiral element, D(OEOEO)$_2$E, has also been synthesized and has shown enantiomeric discrimination as well.[17]

When the dinaphthyl is substituted in the 3,3' position the host has a greater ability to discriminate between the two enantiomers of the guest salt.[16,17,18]

There are very important symmetry properties that these binaphthyl systems possess. The binaphthyl systems have a C_2 or D_2 symmetry group in the molecule. The C_2 or D_2 symmetry groups means that while there are two chiral faces to the macrocycle, above and below the plane of the ring, these chiral faces are identical. (Figure 1) Since the two faces are identical, then approach by the chiral ammonium guest should be equally facile from either side.

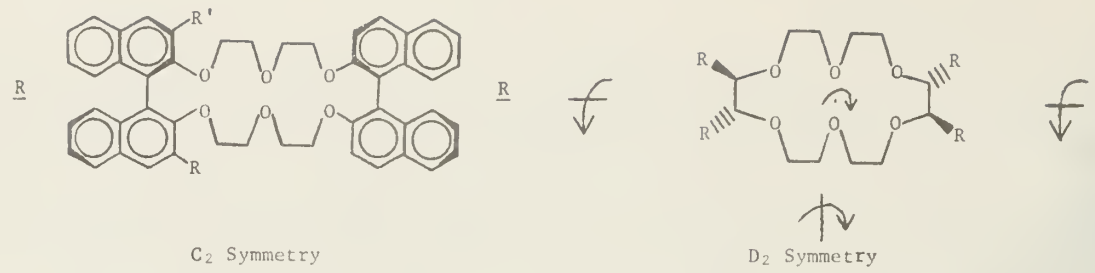


Figure 1. Two representative chiral crown ethers showing C_2 and D_2 symmetry.

Synthesis of these macrocyclic rings can be represented by the following sequence.

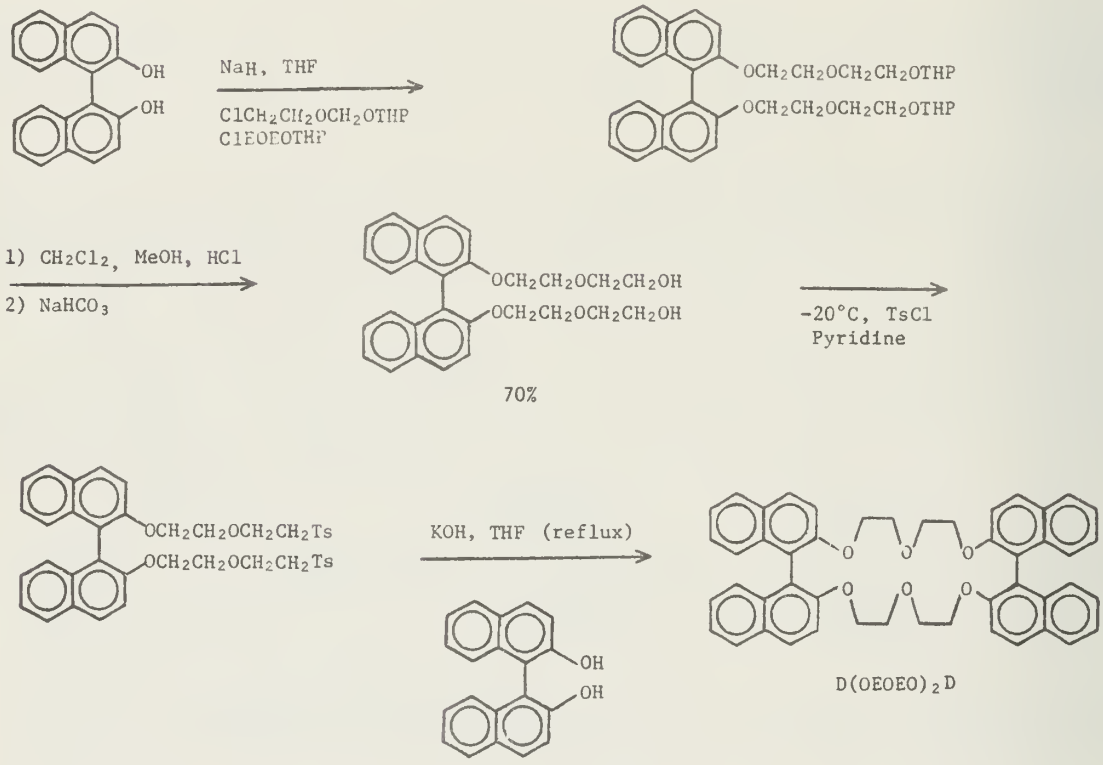
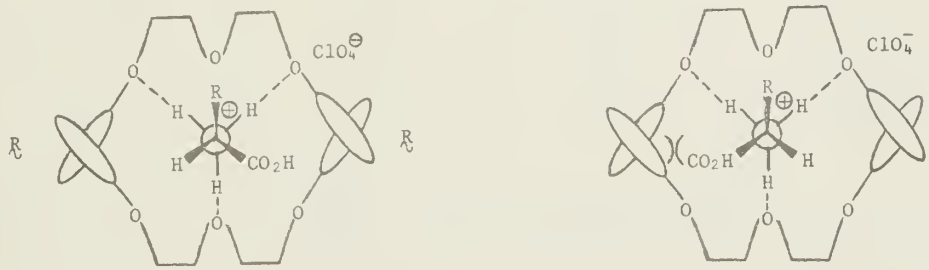


Figure 2. Synthesis of a representative crown ether.

To get optically active macrocyclic hosts, the synthesis must, in most cases, employ optically active starting materials and should not have any steps that could lead to racemization. However in some systems it is possible to crystallize a complex of racemic host with an optically active guest, and after decompostion of the host-guest complex, obtain optically pure host. For example, in the system using 2,2'-dihydroxy-3,3'-diphenyl-1,1'-binaphthyl in the heterocycle $(C_6H_5)_2$D-$(OEOEO)_2$E crystallized with D or L valine ammonium hexafluorophosphate as the guest to give the optically pure host.[17] The enantiomeric resolution of (RR)(SS)-3,3'-$(CH_3)_2$D$(OEOEO)_2$D can be accomplished by allowing the complex of (RR)(SS)-3,3'-$(CH_3)_2$D$(OEOEO)_2$D with D or L-phenylglycinium perchlorate to crystallize.[16] The binaphthyl group can also be resolved by incorporating (RS)binaphthyl and 1,2:5,6-di-O-isopropylidene-mannitol in the macrocyclic ring, then the separation on silica gel of the diastereomers.[13]

Chiral recognition by the chiral crown ethers of 2,2'-dihydroxy-1,1'-binaphthyls is thought to be mainly the result of steric interactions. The recognition model suggested by Cram et al.[16,17,18,19,20,21] has the ammonium hydrogens H-bonding to the ring oxygens, the rest of the molecule then lies in the cavity defined by the binaphthyl groups (Figure 3). From Figure 3 we can see that RR-D is the more stable complex with the $-CO_2H$ group lying along the naphthyl ring.



(R R) - (D) - complex (R R) - (L) - complex

Figure 3. Diastereomeric complexes of $D(OEOEO)_2D$ and racemic amino acid perclorate salts.

In the RR-L complex the $-CO_2H$ group is involved in steric repulsion with the naphthylene ring. If the naphthylene ring is substituted at the 3 and 3' positions the steric interference increases. The 9,9'-spirobifluorene crown ethers are believed to have the same chiral recognition pattern as the binaphthyls.[15,22] The chiral crown ethers using mannitol are also believed to use the same chiral recognition system as binaphthyls and spirobifluorenes.[6]

In examining models of chiral recognition and designing better hosts, accurate measurement of the enantiomeric distribution constant (EDC) and the $\Delta(\Delta G°)$ are needed. The $\Delta(\Delta G°)$ is the difference in the Gibbs free energy of the two different diastereomeric host-guest complexes and can be calculated from equation 1. The enantiomeric distribution constant can be calculated from equation 2 when CRF* is the chiral recognition factor, CSF is the chiral storage factor, $[H \cdot G_aX^*]$ is the concentration of host-guest complex with enantiomer a in organic solution, $[H \cdot G_bX^*]$ is the concentration of host-guest complex with enantiomer b in organic solution, $[G_b]$ is the concentration of enantiomer B in aqueous solution and $[G_a]$ is the concentration of enantiomer A in aqueous solution.

$$(1)\quad \Delta(\Delta G°) = -RT\ln EDC$$

$$(2)\quad EDC = \frac{Ka^A}{K_b^B} = CRF^* \cdot CSF = \frac{[H \cdot G_aX^*][G_b]}{[H \cdot G_bX^*][G_a]}$$

In perhaps simpler terms the EDC describes the distribution of the two enantiomeric guests in the organic phase between the free molecules and their complexes with the host.[16] Table 1 describes the host-guest complexes EDC and $\Delta(\Delta G°)$ as groups at the 3 and 3' position of 2,2'-dihydroxy-1,1'binaphthyl are varied and the R of $RCH(CO_2H)$-NH_3ClO_4 is varied.[16,17]

Table 1.

Enantiomeric distribution constants (EDC) and $-\Delta(\Delta G°)$ values for extraction of racemic $RCH(CO_2H)NH_3ClO_4$ or $RCH(CO_2Me)NH_3ClO_4$ from D_2O into $CDCl_3$-CD_3CN solution as the complex with optically pure host at 0°C.

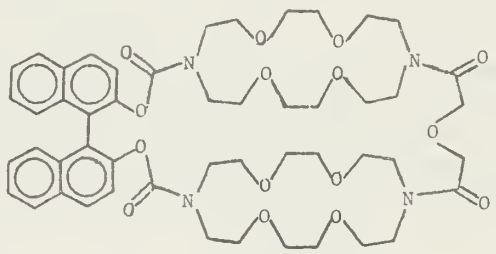
Host formula	R of $RCH(CO_2H)NH_3ClO_4$	Dominant complex formed	EDC[a]	$\Delta(\Delta G°)$[a] Kcal/mole
D(OEOEO)$_2$D	C_6H_5	(RR) (D)	1.7	.3
$(CH_3)_2$D(OEOEO)$_2$D[b]	C_6H_5	(SS) (L)	9.8	1.2
$(CH_3)_2$D(OEOEO)$_2$D[b]	$pOHC_6H_4$	(SS) (L)	9.4	1.2
$(CH_3)_2$D(OEOEO)$_2$D[b]	CH_3	(SS) (L)	2.3	.45

Host formula	R of $RCH(CO_2CH_3)NH_3ClO_4$	Dominant complex formed	EDC[a]	$\Delta(\Delta G°)$[a] Kcal/mole
D(OEOEO)$_2$E	C_6H_5	(R) (L)	1.6	.3
$(CH_2OC_6H_5)_2$D(OEOEO)E[b]	C_6H_5	(S) (L)	3.4	.7
$(C_6H_5)_2$D(OEOEO)$_2$E[b]	C_6H_5	(R) (D)	19.5	1.6
$(C_6(CH_3)_5)_2$D(OEOEO)$_2$E[b]	C_6H_5	(S) (L)	1.3	.2

a. calculated assuming no uncomplexed guest in the organic layer at equilibrium
b. substituted at the 3 and 3' positions

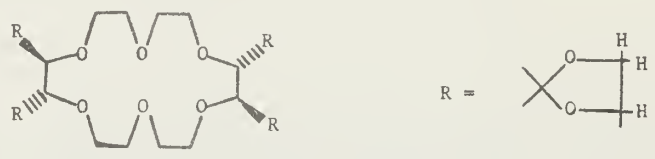
From the table it can be seen that there is an optimum bulk at the 3 and 3' positions for the enhancement of chiral recognition by the host. There is also an increase in selectivity with a larger R group on the amino acid.[16,17] For example when R is CH_3 the $\Delta(\Delta G°)$ was 0.45 Kcal/mole; when R was changed to C_6H_5 the $\Delta(\Delta G°)$ increased to 1.2 Kcal/mole.

A cryptand (2) using binaphthyl as the chiral element achieved an EDC of 1.35 with α-phenethyl ammonium chloride.[17]



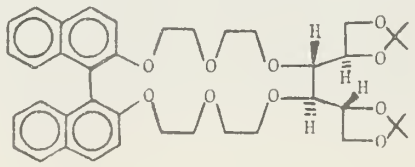
(2)

A host using a modified mannitol (3) achieved an EDC of 1.50 with α-phenethyl ammonium hexafluorophosphate.[12]



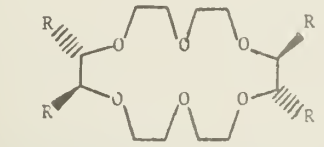
(3)

A mixed system involving a derivative of D-mannitol and 2,2'-dihydroxy-1,1'-binaphthyl (4) achieved an EDC of 1.63 with α-phenethyl ammonium hexafluorophosphate.



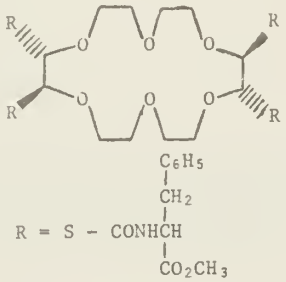
(4)

Two systems involving modified tartaric acid in polymeric membranes have been examined by Lehn et. al.[8] and Yasaka et. al.[23] using enantiomeric selective electrodes[24,24] to determine the EDC. With Lehn's system (5) an EDC of 2.57 was reported with the R enantiomer favored. With Yasaka's system (6) an EDC of 1.17 was observed again with the R enantiomer favored. Both systems used racemic α-phenethyl ammonium chloride for their guest.



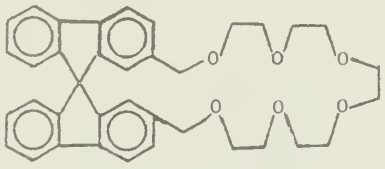
R = $CON(CH_2CH_2CH_2CH_3)_2$

(5)



(6)

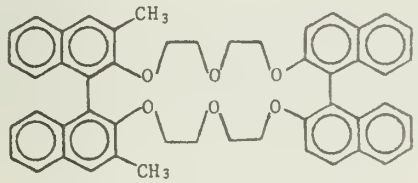
The 9,9'-spirobifluorene system (7) has been synthesized and shows an EDC of about 2.33[15,25] with α-phenethyl ammonium chloride. The EDC was measured with an enantiomeric selective electrode.[24,25]



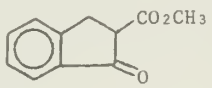
(7)

A possible use for chiral crown ethers would be to use them as chiral catalysts.

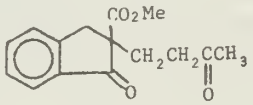
Cram and Sogah used a substituted binaphthyl macrocycle (8) to catalyze a Michael reaction in high chemical and optical yields. Using 1-indanone-2-methyl-carboxylic



(8)

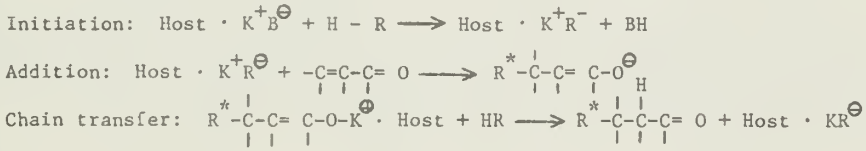


(9)



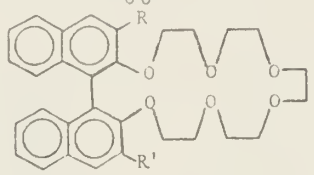
(10)

ester (9) with methyl vinyl ketone, potassium t-butoxide and host (8) at -78°C gave R 10 in 48% yield and 99% enantiomeric excess, at 25°C with the same reagents, the yield was 75% and the enantiomeric excess was 67%. The mechanism proposed by Cram to account for the high optical yield is outlined below.



Because the indanyl anion is complexed inside the host, stereocontrol can be achieved through steric hindrance to the approach of the methyl vinyl ketone.

Cram has also studied transacylation of amino ester salts with a modified binaphthyl heterocycle as host.[27] (11)



R = CH_2SH

(11)

Table 2 records the rate constants for the liberation of p-nitrophenol from α-amino esters of p-nitrophenol in the presence of (R)(S)-11.

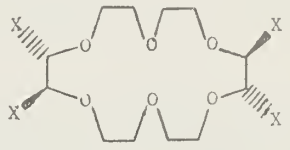
Table 2.

Rate comparison for liberation of p-nitrophenol from 10^{-4}M solution of amino ester salts in the presence of 5.0 x 10^{-3}M. 11 at 25°C in 20% EtOH, CH_2Cl_2(v/v) buffered with .3M AcOH and .1M $(CH_3)_4N^{\oplus}OAc^{\ominus}$.

Run#	Polyether present	R in $RCH(NH_3^{\oplus})CO_2Ar \cdot Br^{\ominus}$	Configuration	10^3k, s^{-1}	rate factor
1	(S)-10	CH_3	L	70	1
2	(R)-10	CH_3	L	70	
3	(S)-10	$(CH_3)_2CHCH_2$	L	~70	~6
4	(R)-10	$(CH_3)_2CHCH_2$	L	11	
5	(S)-10	$C_6H_5CH_2$	L	340	8.3
6	(R)-10	$C_6H_5CH_2$	L	41	
7	(S)-10	$C_6H_5CH_2$	D	42	8.1
8	(R)-10	$C_6H_5CH_2$	D	340	
9	(S)-10	$(CH_3)_2CH_2$	L	22	9.2
10	(R)-10	$(CH_3)_2CH_2$	L	2.4	

a. Pseudo-first-order rate constants corrected for buffer solvolysis, made in triplicate runs of 14 points each, and followed by the appearance of $NO_2C_6H_4$-OH at 345 nm.

Lehn and Sirlin[28] have also studied thiolysis reactions with a modified tartaric acid heterocycle as the host (12). When the enantiomeric dipeptide ethers glycine-L-phenylalanine-O-p-nitrophenyl ether and glycine-D-phenylalanine-O-p-nitrophenyl ester were used with the chiral host, high chiral discrimination was observed.

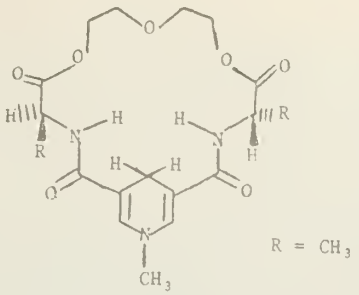


X = CONH - (L) - $CH(CH_2SH)$ CO_2Me

(12)

The L-enantiomer reacts about 50-90 times faster with 12 than does the D-antipode.

Asymmetric reductions of a prochiral ketone with a chiral host have also been reported. When the chiral host was the substituted 1,4-dihydropyridine crown ether (13) enantiomeric excesses of 64-86% were observed with 65-82% NMR yields. With trifloroacetophenone the isolated yield was 58% and the optical yield was 68%.



(13)

It was brought to my attention as the manuscript was being prepared that a review of this material has been published recently in the Journal of Heterocyclic Chemistry.[30]

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MECHANISMS OF REACTIONS OF (2-CHLOROETHYL)NITROSOUREAS

Reported by David M. Simpson

November 1, 1982

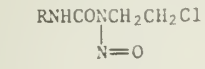
Biological Implications

The N-(2-chloroethyl)-N-nitrosoureas (CENUs) have been clinically useful in the treatment of a broad range of human malignancies.[1,2] The major limitations to their clinical use are their delayed and cumulative toxicities.[3] One great advantage of the CENUs over other types of anticancer agents is that they have an appropriate lipid solubility to cross the "blood-brain barrier" and kill intracerebral neoplastic cells.[4,5,6]

Syntheses and structure-activity analyses of many congeners of CENUs have been performed.[7]

The reaction products of biomolecules and the CENUs have been extensively studied. In general, the 2-chloroethyl group alkylates nucleic acids and proteins, whereas an isocyanate group almost exclusively cabamoylates proteins;[9-11] antitumor activity depends mainly on the alkylating activity.[7d]

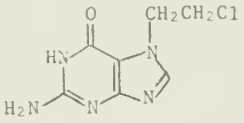
Polyribonucleotides and DNA react with BCNU 1 to give O- and N-modified bases which may be isolated by high pressure liquid chromatography and identified.[12] Examples of these modified bases are compounds 2 - 6. The β-chloroethylated bases such as 2 and



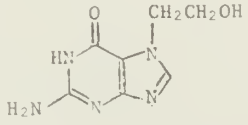
1, R= CH_2CH_2Cl

7, R= C_6H_{11}

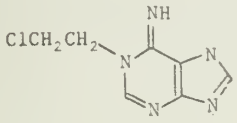
8, R= trans-4-$CH_3C_6H_{10}$



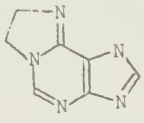
2



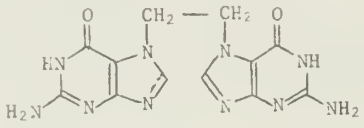
3



4



5



6

4 are presumably intermediate in the formation of the ethylene-bridged bases such as 6, which may be formed by nucleophilic substitution for the halogen.[13,14] This capability is of great biological interest, as it allows a mechanism for DNA-interstrand and DNA-protein cross-links. These reactions, as well as monoalkylation of DNA, may lead to DNA lesions and cell death. Also of interest are the β-hydroxethylated bases such as 3. The corresponding β-chloroethylated bases are only slowly hydrolyzed, so another mechanism to explain their formation is required.

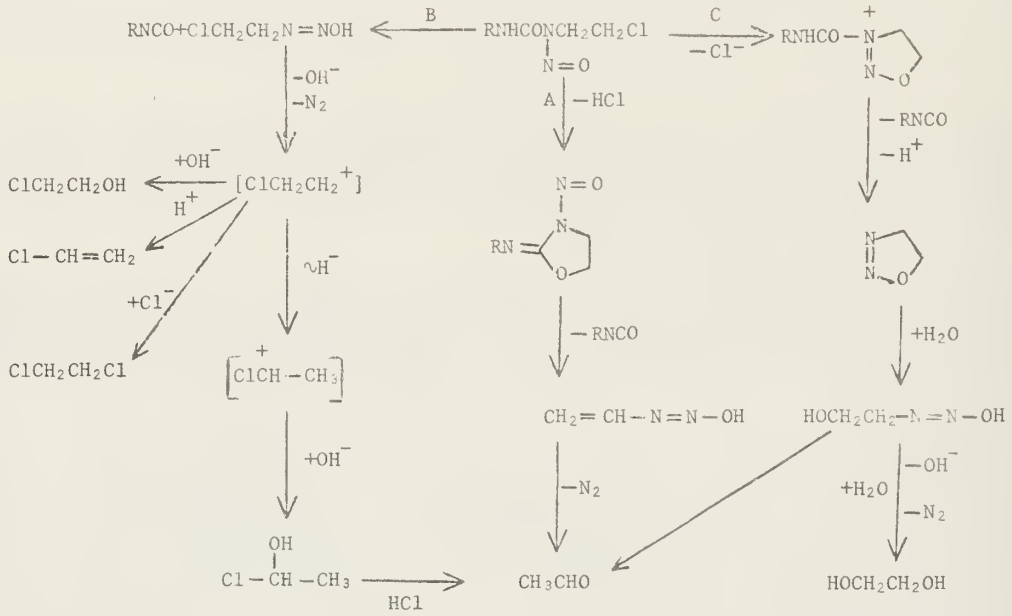
The remainder of this paper will discuss the pathways in the conversions of CENUs to their reactive intermediates and final products, and the factors which favor particular pathways. These reactions are usually performed in phosphate buffered aqueous

olutions at approximately neutral pH and at or just above room temperature in order to simulate to some degree in vivo conditions. It has also been found that the presence of phosphate catalyzes reaction and alters the major product of reaction of CENU from acetaldehyde in distilled water to 2-chloroethanol in the phosphate buffered solution.[15]

Mechanisms of Reaction, Pathway B

There are at least three major pathways in the aqueous reactions of CENUs, pathways A, B, and C in Scheme 1.

Scheme 1.



Pathway B was proposed very early in these mechanistic studies to explain the formation of carbamoylating and alkylating species. There is considerable experimental support[14,16-19] and little dispute that it is the major source of chloroethylating species. The first step in pathway B for the reaction of 1 is abstraction of the NH proton. Concomitant with or just subsequent to this abstraction 1 breaks down into (2-chloroethyl)diazohydroxide and (2-chloroethyl)isocyanate. Subsequent reaction of the diazohydroxide can afford 2-chloroethanol, vinyl chloride, 1,2-dichloroethane, and acetaldehyde.

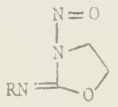
Pathway A

The reactions of 1 and of CCNU 7 in water yielded, along with N_2 and the products expected from the intermediate isocyanate, primarily acetaldehyde and HCl rather than 2-chloroethanol.[20] Dehydrochlorination of 2-chloroethanol to produce acetaldehyde was shown not to occur under the reaction conditions, so pathway A was postulated as a possible source of acetaldehyde. Nucleophilic attack of the carbonyl oxygen on the β-carbon results in cyclization to give the 2-(alkylimino)-3-nitrosooxazolidine with loss of HCl, followed by decomposition to (ethylene)diazohydroxide and (2-chloroethyl) isocyanate. The (ethylene)diazohydroxide gives vinyl alcohol which rearranges to acetaldehyde.[15] Evidence for the intermediacy of the (ethylene)diazohydroxide is the identification of vinyl bromide after reaction in the presence of sodium bromide.[21]

Three examples of the intermediate 2-(alkylimino)-3-nitrosooxazolidines which should be produced from 1, 7, and MeCCNU 8, that is 9, 10, and 11, have been synthe-

ed in unlabelled[22] and specifically deuterated[22] forms, and the products of their reaction in phosphate buffered solutions at pH 7.2 have been examined by physical, spectral, and biological methods.

An assay measuring DNA alkylation by electrophiles using fluorescence techniques was used to compare the reactivities of the nitrosooxazolidines and their parent CENUs; in each case comparable alkylating activity was observed.[22] The nitrosooxazolidines were stable in the solid form or in aprotic solvents. However, they decomposed slowly in protic solvents and rapidly in buffer solutions in the presence of Cl^- to give the products found after decomposition of the parent CENUs. In addition, treatment of 10 and 11 with HCl affords the parent CENUs. These results support the scheme placing the nitrosooxazolidines as intermediates in pathway A.



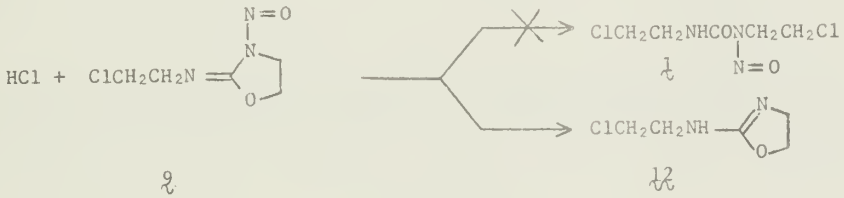
9, R= $ClCH_2CH_2$

10, R= C_6H_{11}

11, R= trans-4-$CH_3C_6H_{10}$

The nitrosooxazolidine 9, expected to open to give 1 upon treatment with HCl, was instead quantitatively denitrosated to give the oxazoline 12, Scheme 2. This anomalous behavior was attributed to a different preferred site for protonation in 9 versus 10 and 11.[22]

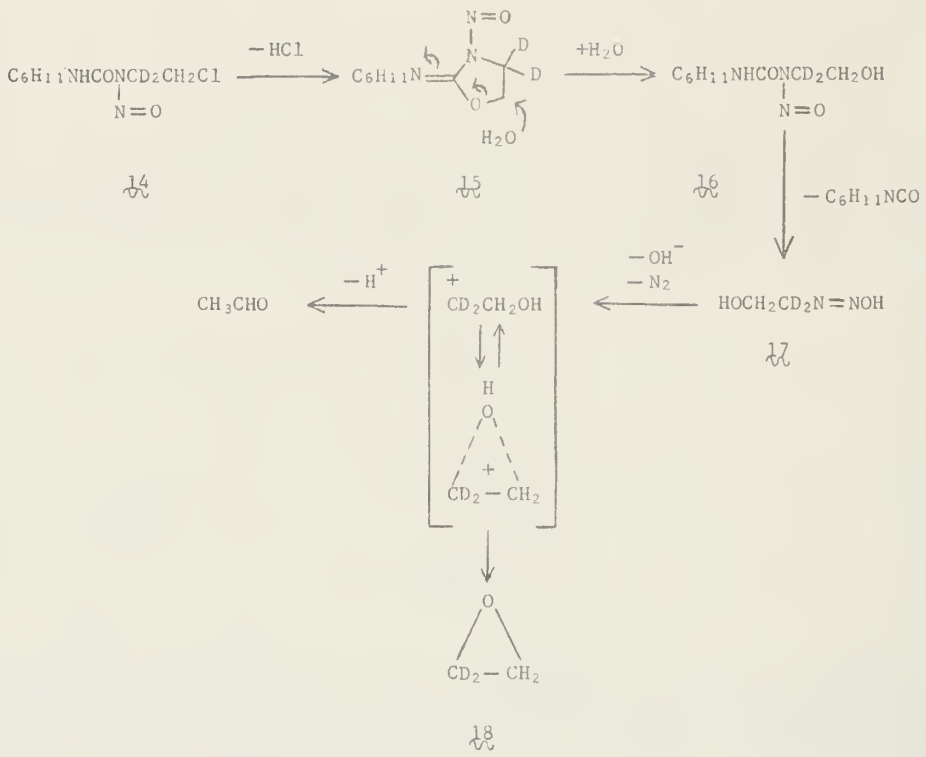
Scheme 2.



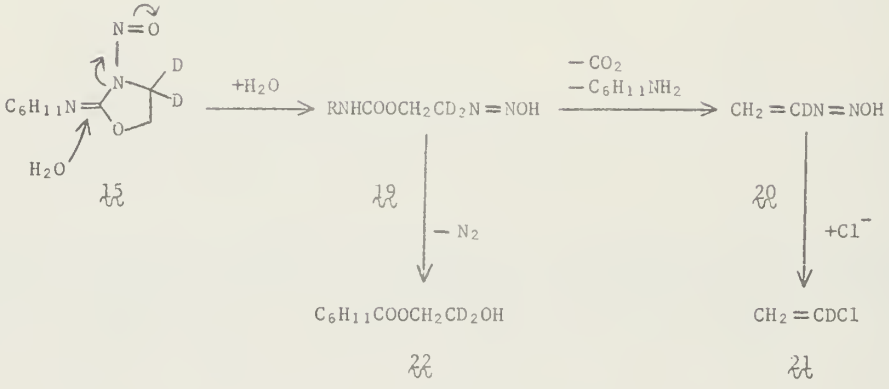
It is plausible that pathway B produces only minor amounts of acetaldehyde, because the (2-chloroethyl)diazohydroxide and 2-chloroethyl cation are susceptible to trapping before the hydride shift occurs. Reaction of 7 yields 5-10% acetaldehyde, and reaction of 10 leads to an 8-10% yield of acetaldehyde, whereas reaction of the (2-hydroxyethyl)nitrosourea analog 13 of 10 leads to 25-35% yield of acetaldehyde.[23] It was suggested that for the deuterium labelled compounds 14 may cyclize to 15 which opens to 16 via nucleophilic attack of water at carbon-5, Scheme 3.[23] Compound 16 may then lose the isocyanate to give the (2-hydroxyethyl)diazohydroxide 17 which can lose N_2 and H_2O to form acetaldehyde. This scheme receives support from the detection of oxirane-2,2-d_2 18 as a minor product of the reaction of 15, which may arise from the oxiranium ion afforded from 17 or its cationic equivalent. The (2-hydroxyethyl)-diazohydroxides could account for the formation of the hydroxyethylnucleosides which are produced by decomposition of the CENUs in the presence of polynucleotides.[12]

Another product of decomposition of 15 in the presence of Cl^- was the monodeuterated vinyl chloride 21, Scheme 4. The position of the label cannot be explained by the mechanism of pathway B. A plausible pathway is the formation of the 2-hydroxydiazoethyl cyclohexylcarbamate 19 by attack of water at carbon-2 of 15 followed by elimination to give the (ethylene)diazohydroxide 20. Substitution by Cl^- gives the appropriatedly deuterated 21.

Scheme 3.

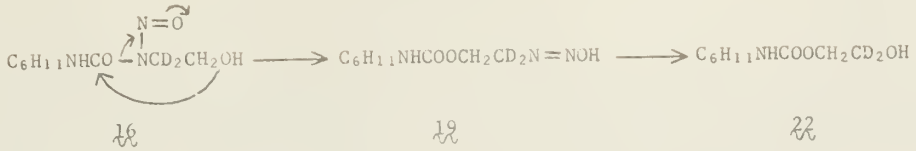


Scheme 4.



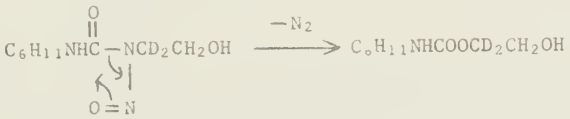
Another minor product of the reaction of 14 and of 15 was a mixture of the hydroxyethyl carbamates, β-d_2 22 in Scheme 4 and 5 as the major isomer and α-d_2 23 in Scheme 6 as the minor isomer. The formation of the major isomer may be by hydrolysis of the hydroxydiazo moiety of 19 in Scheme 4 or by intramolecular attack of the hydroxyl group on the carbonyl of 16 with cleavage of the (CO)-N(NO) bond to give 19, followed by hydrolysis and loss of nitrogen, as shown in Scheme 5. The minor isomer 23 may arise from a 1,3-nitrogen-to-oxygen rearrangement in 16, followed by elimination of N_2, Scheme 6.

Scheme 5.



16 19 22

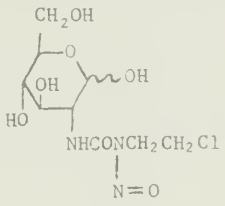
Scheme 6.



16 23

Pathway C

Based on kinetic evidence, pathway C of Scheme 1, which proceeds through a second cyclic intermediate, was proposed.[24] Intramolecular substitution forms the acyl oxadiazolinium ion, which loses an isocyanate to form the 1,2,3-oxadiazoline. Hydrolysis of the N-O bond gives a (2-hydroxyethyl)diazohydroxide, which can afford acetaldehyde or ethylene glycol. A 5 to 4 deuterium shift occurs at some point in the decomposition, as evidenced by the appearance of $CH_2DCDH^{16}OH$ as well as $CH_3CDH^{16}OH$ when BCNU-B,B'-d_4-$N^{16}O$ was reacted in $H_2{}^{18}O$ and the acetaldehyde was "fixed" by reduction with horse liver alcohol dehydrogenase.[25] The proposal of the mechanism was based on studies of the reaction of chlorozotocin 24 which showed that, although the total amount of Cl^- produced generally decreased with increasing pH, the hydrolytic rates determined by either loss of UV absorbance of the nitroso moiety or Cl^- production were the same at each pH value. This result indicates that the reactions which result in loss of Cl^- and loss of the nitroso group are not necessarily the same. The intermediacy of the nitrosooxazolidine is suggested by the result that the non-nitrosated urea analog of 24 affords free Cl^- at a rate comparable to 24 in buffer at pH 4.0. How-



24

ever the yield of Cl^- from the urea was only 40%, whereas the yield from 24 was 90%. This suggests that the nitroso oxygen is the primary cyclizing nucleophile for 24. Also, it was argued, the loss of NO from the nitrosooxazolidine would have to be instantaneous so that the rates observed by UV changes and Cl^- liberation will agree; the nitrosooxazolidines are not necessarily that unstable. The mechanism via the oxadiazole satisfactorily explains the similar rate constants.

The cyclic pathways A and C have been shown by kinetic experiments and product analyses to predominate at lower pH, and pathway B at higher pH.[24,26] The shift in mechanisms may be due to the fact that the rate-limiting reaction to form (2-chloroethyl)diazohydroxide in pathway B is base catalyzed and at lower pH becomes slower than the cyclizations of pathways A and C.

It is possible to discriminate between the relative contributions that pathways A and B and pathway C make in the decomposition of CENUs.[25] This scheme relies on the fact that carbonyl compounds are among the products of CENU decompositon according to the three pathways. Oxygen-18 from solvent $H_2{}^{18}O$ should be incorporated in the acetaldehyde resulting from decomposition of CENUs by pathways A and B. The oxygen in the acetaldehyde produced via pathway C should originate in the nitroso group and therefore should remain the ^{16}O isotope. In order to prevent O exchange of the product carbonyl compounds the oxygen was "fixed" by reduction with horse liver alcohol dehydrogenase. Decompostion of BCNU-β,β'-d_4 in phosphate buffered 99% $H_2{}^{18}O$ at pH 7.1, 25°C afforded 79% ethanol-d-^{18}O and 21% ethanol-d-^{16}O, thus suggesting a 21% contribution via the 1,2,3-oxadiazoline intermediate.

In contrast to 1 decomposition, BCNU-α,α'-dimethyl under the same conditions exhibited approximately 89% contribution by pathway C. This preference may indicate the stabilizing effect of the α-methyl group on the intermediate diazohydroxides or cation equivalents of pathways A and B, which disfavors the hydride shift required to form the aldehyde.

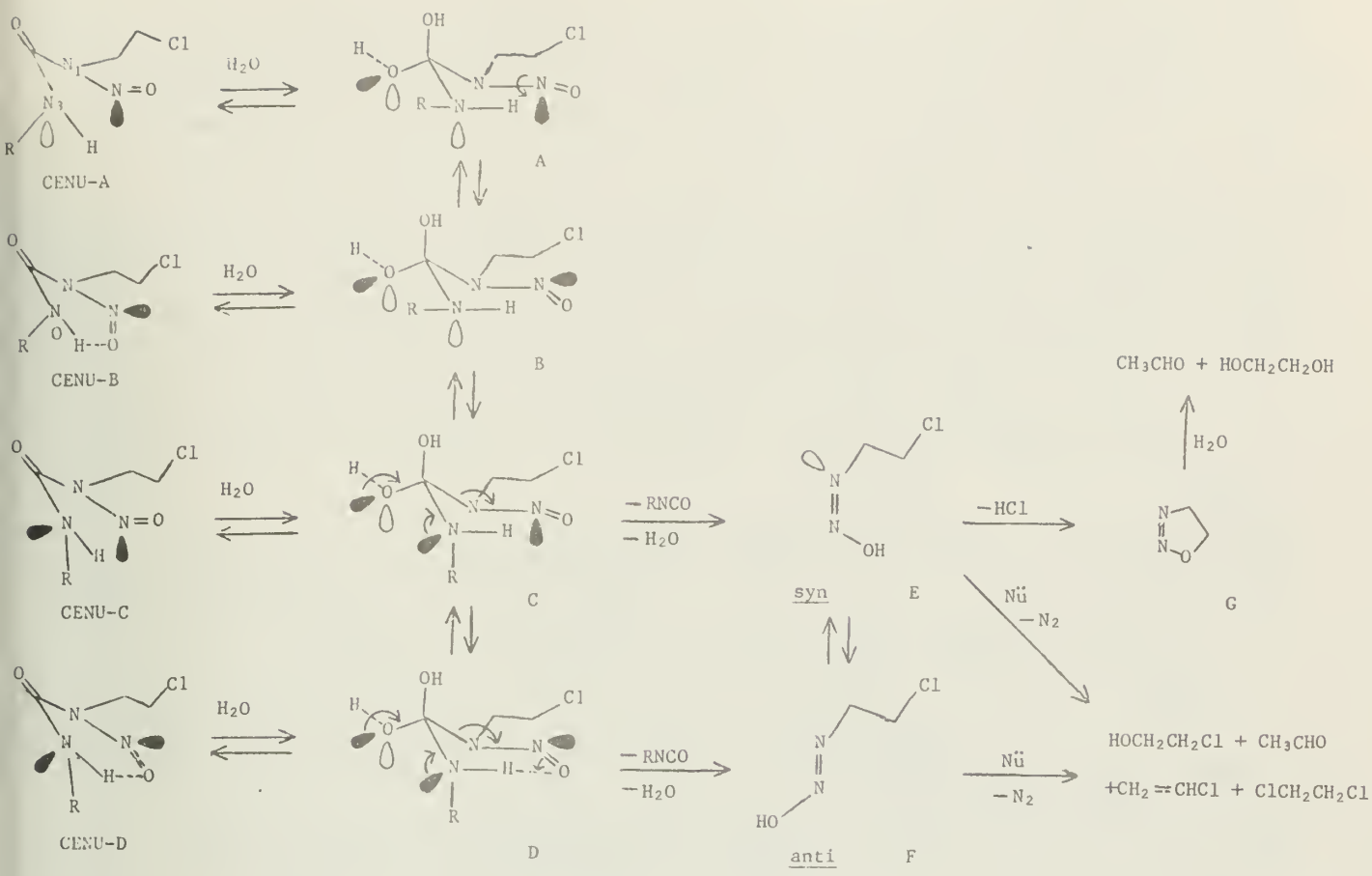
Stereoelectronic Control?

Spectral studies of the conformations of CENUs labelled with ^{15}N, ^{13}C, and ^{2}H have been performed.[21] A proposal was then made by the authors to relate their results to their model for stereoelectronic control in the reactions of CENUs.

When in nonpolar aprotic solvents CENUs adopt a preferred conformation in which the nitroso group is aligned towards the 2-chloroethyl group, CENU-A in Scheme 7. No three bond coupling between the ^{15}NO nitrogen and the proton α to N_1 occurs in either $CDCl_3$ or Me_2SO-d_6; however, this may be due to noncoplanarity of the nitroso group and the α hydrogens of the 2-chloroethyl groups. Further support is the fact that the carbons of the nitroso-bearing side chain of 1 resonate at higher field than the carbons of the other side chain. The large coupling constant between the ^{15}NO nitrogen and the ^{13}CO carbon and the small coupling constant of the ^{15}NO nitrogen and the ^{13}C α to N_1 were also said to be indicative of a "W" conformation.

The chemical shifts and coupling constants of the CENUs change with both solvent polarity and basicity. The ^{1}H shifts of the CH_2 groups α to N_1 change little upon increasing the solvent polarity. The CH_2 group α to Cl undergoes a progressive downfield shift. The amide ^{15}N resonances shift downfield upon increasing the solvent polarity, which has been attributed to an increase in π bond order of the C-N bond and π charge density on nitrogen, in addition to solvent effects. The coupling constants for $^{15}N_3$-^{13}CO are higher in the CENUs than in the ureas, indicating more delocalization of the N_3 lone pair in the CENUs as compared to the ureas, whereas the $^{15}N_1$-^{13}CO coupling constants for the CENUs are lower than for the ureas, indicating less extensive delocalization of the N_1 lone pair into the acyl group. Changing the solvent from $CDCl_3$ to Me_2SO-d_6 causes a decrease in the $^{15}N_3$-^{13}CO coupling constant and an increase in the $^{15}N_1$-^{13}CO coupling constant. These changes suggest a decrease in the $^{15}N_3$ lone pair delocalization and an increase in the $^{15}N_1$ lone pair delocalization into the acyl group. A downfield shift of the ^{15}NO resonance also occurs upon increasing the solvent polarity and basicity which the authors explained as due either to rotation about the N-N bond or due to solvent interaction with the nitrogen lone pair. Rotation about the N-N bond was also said to be supported by the fact that the two-bond coupling between the ^{13}CO carbon and the ^{15}NO nitrogen and the three bond coupling between the hydrogens on the carbon α to N_1 and the ^{15}NO nitrogen vary with the solvent changes.

Scheme 7.



The conformational changes of 1 and 7 and the possibility of hydration of the carbonyl group were examined. No hydration of the carbonyl carbon to a stable sp^3 hybridization was observed in the ^{13}C-NMR spectrum at ambient temperature between pH 5.2 and 5.0; however, a new signal slightly downfield from the original signal appeared and grew at the expense of the original at 31°C and was attributed to slow formation of a new rotamer, CENU-C in Scheme 7. During this change new peaks assignable to decomposition products appeared. The conformational changes were slower in dioxane-phosphate buffer than in methanol-phosphate buffer, and did not occur in nonpolar aprotic solvents. Incubation of ethyl N-(2-chloroethyl)-N-nitrosocarbamate in dioxane-^{18}O enriched water at pH 7 gave incorporation of ^{18}O into the carbonyl group but not the nitroso group.

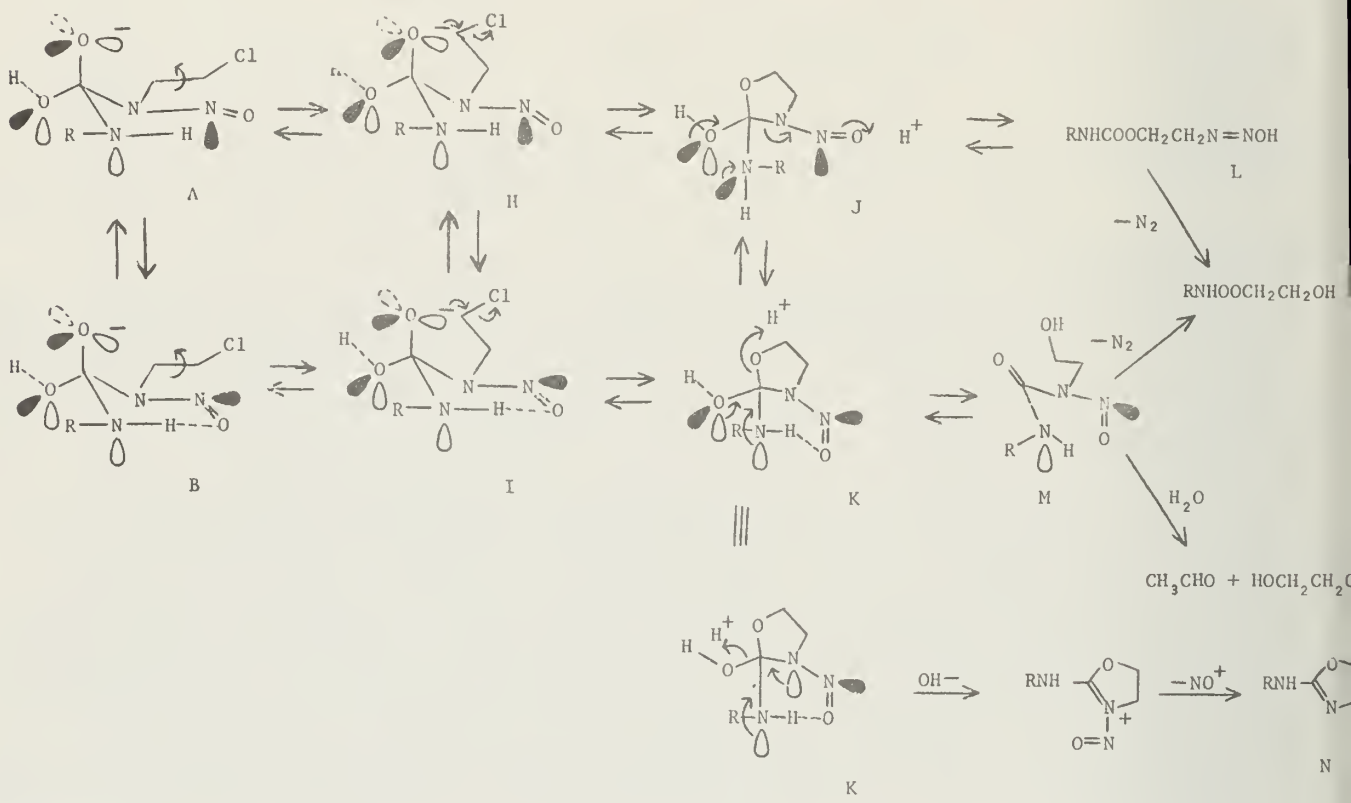
It was concluded by the authors, therefore, that conformational changes of CENUs occur via tetrahedral intermediates in which there is substantially less N_1-CO π bond character to hinder rotation and also less N_3 lone pair delocalization so that N_3 inversion can occur more readily.

A model for stereoelectronic control in the pH dependant decomposition of CENUs was proposed by the authors.[21] The stereoelectronic factors that control the cleavage of a tetrahedral intermediate require: (1) specific cleavage of a C-O or C-N bond occurs when two heteroatoms of the tetrahedral intermediate each have an orbital oriented antiperiplanar to the departing O-alkyl or N-alkyl leaving group, (2) when a tetrahedral intermediate cannot break down with stereoelectronic control, the energy barrier for its cleavage becomes larger than that for rotation to give other conformers.

The conformation CENUs adopt in the solid state and in nonpolar aprotic solvents is that of CENU-A in Scheme 7. Hydration gives A, rotation to B follows, and then dehydration gives CENU-B, the conformation that CENUs adopt in aqueous solutions. Rotation from B can give C, or N_3 inversion of A can give C. In C the lone pair orbitals on both heteroatoms are aligned antiperiplanar to the CO-N_1 bond, thus cleavage can occur to give the syn-(2-chloroethyl)diazohydroxide E. Compound E is correctly aligned for intramolecular nucleophilic substitution to give the 1,2,3-oxadiazoline G. Cleavage of D affords the anti-(2-chloroethyl)diazohydroxide F. Either E or F may react with various nucleophiles to yield 2-chloroethanol, acetaldehyde, vinyl chloride, and 1,2-dichloroethane.

Further conformational changes may occur, Scheme 8. Rotamers A and B may rotate to give H and I, which are aligned in the proper fashion to give the nitrosooxazolidines J and K. Compound J may decompose to the 2-(hydroxydiazo)ethyl carbamate L by C_2-N_3 bond cleavage. Compound K may decompose to give the (2-hydroxyethyl)nitrosourea M. Compound K may also decompose to give the denitrosated product N.

Scheme 8.



Summary

The three mechanisms of reaction of N-(2-chloroethyl)-N-nitrosoureas in aqueous phosphate buffered solutions have been described. The products of these reactions can subsequently react with biomolecules. A model for stereoelectronic control in the reaction of the CENUs was proposed[21] in an attempt to explain the distribution of products afforded from the reaction of CENUs. This model contains several flaws: (1) the nitrosourea is depicted in a pseudo chair conformation whereas a planar form maximizing delocalization is preferable, (2) the nitrogens are depicted with sp^3 hybridization instead of with sp^2 hybridization with p orbitals undergoing π bonding, (3) there should be increased delocalization of the N_1 lone pair into the NO moiety in the hydrated CENU which should hinder N-NO rotation, (4) the crucial carbonyl ^{13}C NMR peak which grows in polar solvents was attributed to an unisolated conformational isomer of the original CENU, whereas the concomitant appearance of other carbonyl ^{13}C NMR signals assignable to reaction products suggests that this signal may be that of another reaction product.

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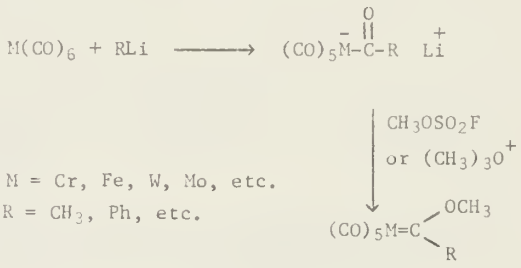
1. Acronyms commonly used in the literature are: BCNU, 1,3-bis-(2-chloroethyl)-1-nitrosourea; CCNU, 3-cyclohexyl-1-(2-chloroethyl)-1-nitrosourea; MeCCNU, 3-(trans-4-methylcyclohexyl)-1-(2-chloroethyl)-1-nitrosourea. The methylenes progress outward from α to β on the nitrosated side of the urea and from α' to β' on the non-nitrosated side.
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SYNTHESIS OF CYCLOPROPANES USING METAL-CARBENE COMPLEXES

Reported by Dave Lee November 11, 1982

The first stable metal-carbene complex[1,2,3] was synthesized by Fischer and Mäasbol in 1964. They found that metal carbonyls react with organolithium reagents to produce acyl metal anions which could be alkylated on oxygen to give metal-carbene complexes (Scheme I).

Scheme I



Metal-carbene complexes have the following characteristics: (1) while they should not be considered as a source of free carbenes,[4,5] they act as carbene-equivalent functional groups which can be synthesized, modified and converted into other functional groups; (2) they are almost all both thermally stable (over 100°C)[6b,c] and moderately air-stable (although solutions are slowly air oxidized;[6] (3) they are very soluble in organic solvents but not in H_2O[6] even though they have large dipole moments;[7] (4) X-ray determination of the crystal structures of several carbene complexes[8] confirmed the double-bond character (for example, Fig 1); (5) even though the

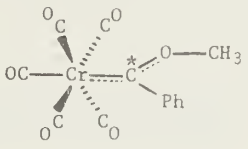
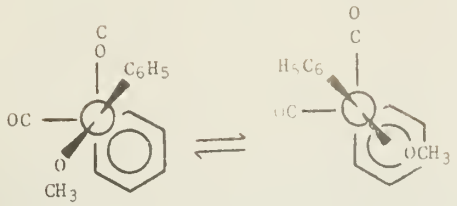


Fig 1

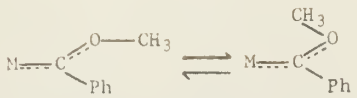
The bond length for Cr-C* (2.04 Å) is shorter than the usual Cr-C single bond (2.21 Å) and also the $*CO_3$ bond length (1.33 Å) is shorter than the usual C-O single bond (1.46 Å).

^{13}C-NMR spectra of carbene complexes are characterized by deshielding of the carbene carbon atom,[9] for example 360 ppm downfield from TMS for $(CO_5Cr{=}C^{*}(OCH_3)CH_3)$ but 212 ppm for $^{+}C(Ph)_3$, they are still not readily interpreted; (6) rotation about the carbene carbon-metal partial double bond is very rapid. This is expected since the carbon p orbital can interact with either of two orthogonal d orbitals on the metal and the net d-p overlap does not vary with rotation. The ^1H NMR spectrum of $(C_6H_6)Cr(CO_2{=}C(OCH_3)C_6H_5)$ (1) shows only one CH_3 peak at low temperature which provides evidence for rapid interconversion of these rotamers (Fig 2a).[25] A rapid interconversion of the CH_3 groups in Fig 2b also occurs at this temperatures.[10,26]



1a 1b

Fig 2a



1c 1d

Fig 2b

The most useful and general procedure for the direct synthesis of metal-carbene complexes is shown in Scheme I. Other direct syntheses[8,11] are summarized as below:

(A) The reaction of diazoalkene precursors with metal complexes[12]

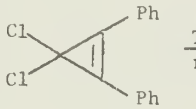
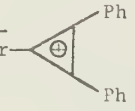
$(CH_3C_5H_4)Mn(CO)_2(THF) + C_6H_5(CO)CN_2C_6H_5$

$\xrightarrow[r.t.]{THF}$ $(CH_3C_5H_4)(CO)_2Mn{=}C(C_6H_5)(C(=O)C_6H_5)$ (37%) m.p. 90.5°C

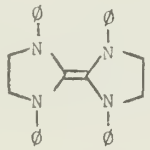
(B) Alkylation of acyl complexes[13]

$Et_2NC(=O)Hg-C(=O)NEt_2 \xrightarrow{2(CH_3)_3O^+}$ $[(CH_3O)(Et_2N)C{=}Hg{=}C(OCH_3)(NEt_2)]^{2+}$ m.p. 202°C

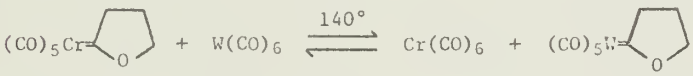
(C) Reactions of metal carbonyl anions[14]

$Na_2Cr(CO)_5 +$  $\xrightarrow[r.t.]{THF}$ $(CO)_5Cr^-$  (19.5%) m.p. 199-200°C

(D) Alkene scission reactions[15]

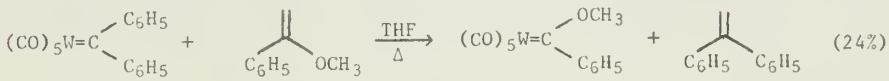
$[(Et_3P)PtCl_2]_2 +$  $\xrightarrow{205°}$ $2(Et_3P)Cl_2Pt{=}C(C_6H_5)N(C_6H_5)$ (100%) m.p. >308°C

(E) Carbene transfer reactions[10]



(Keq=3)

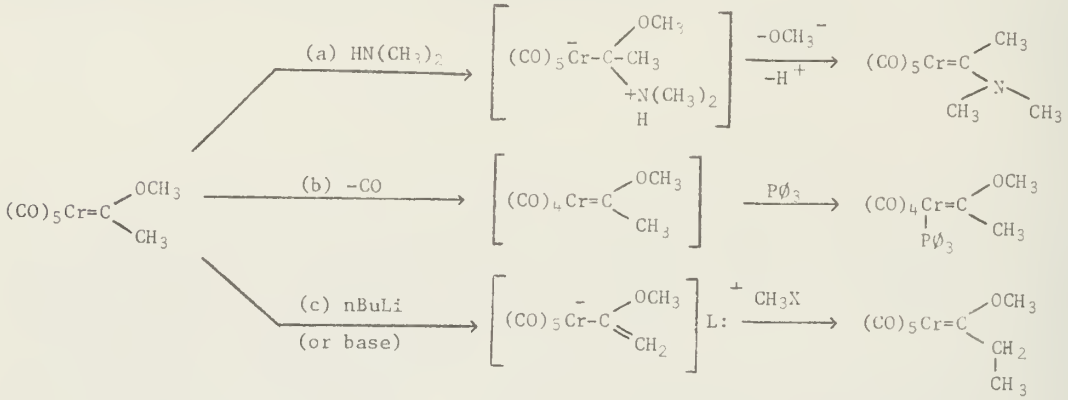
(F) Olefin metathesis[16]



(24%)

In addition to the direct syntheses of metal-carbene complexes, a variety of methods for modifying the structure of carbene complexes has been developed. Three reactive centers in a carbene complex can be used in designing a synthesis of a new carbene complex. For example, $(CO_5)Cr{=}C(OCH_3)(CH_3)$ can be converted into a wide range of carbene complexes by (a) nucleophilic attack at the carbene carbon atom followed by loss of methoxide, (b) ligand substitution reactions in which CO is replaced by a new ligand, and (c) reactions involving anions generated alpha to the carbene carbon atom (Scheme II).

Scheme II

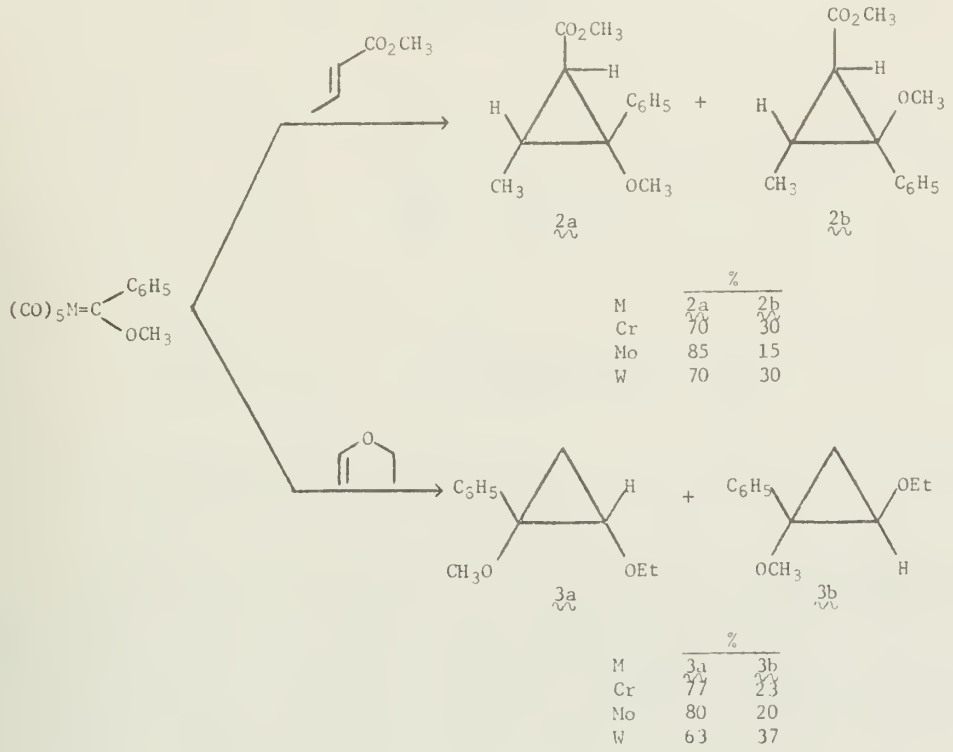


Current routes to alkylcyclopropanes via intermolecular transfer of alkylcarbenes to alkenes are usually limited by low yields. The poor yields are due, in large measure, to competition from intramolecular rearrangements of the non-metal carbenes. These isomerizations include 1,2-hydrogen or -alkyl migrations to give alkenes and insertions to β and more remote C-H bonds to form cycloalkanes.[18,19] Metal-carbene complexes are attractive candidates for reagents to be used in an effort to develop high yield, one-step synthetic procedures for cyclopropanes.

Fischer had found[20] that alkoxy-substituted metal-carbene complexes formed cyclopropanes only upon reaction with two vastly different classes of alkenes, electron-defficient α,β-unsaturated esters and electron-rich vinyl ethers (Scheme III).

All cyclopropanes are formed stereoselectively but the ratio of isomers (2a/2b or 3a/3b) depends on the metal. The metal dependence provides evidence that cyclopropane formation does not involve a free carbene. Since Fischer's studies, numerous carbene complexes have been explored as cyclopropanating agents,[21-28] such as $(CO)_5W{=}C(Ph)(H)$ (4),[21] $(CO)_5W{=}C(Ph)(Ph)$ (5),[16] $(C_5H_5)(CO)_2Fe{=}C(H)(R)$ (6),[22] etc. Among them, 4 has been most widely investigated.[11,21]

Scheme III

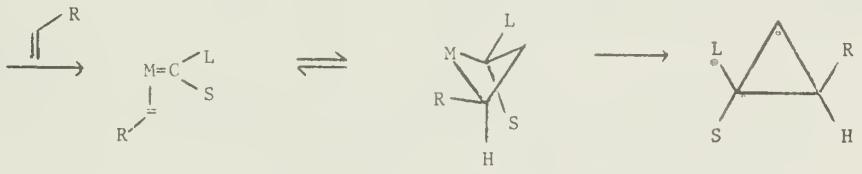


M	% 2a	2b
Cr	70	30
Mo	85	15
W	70	30

M	% 3a	3b
Cr	77	23
Mo	80	20
W	63	37

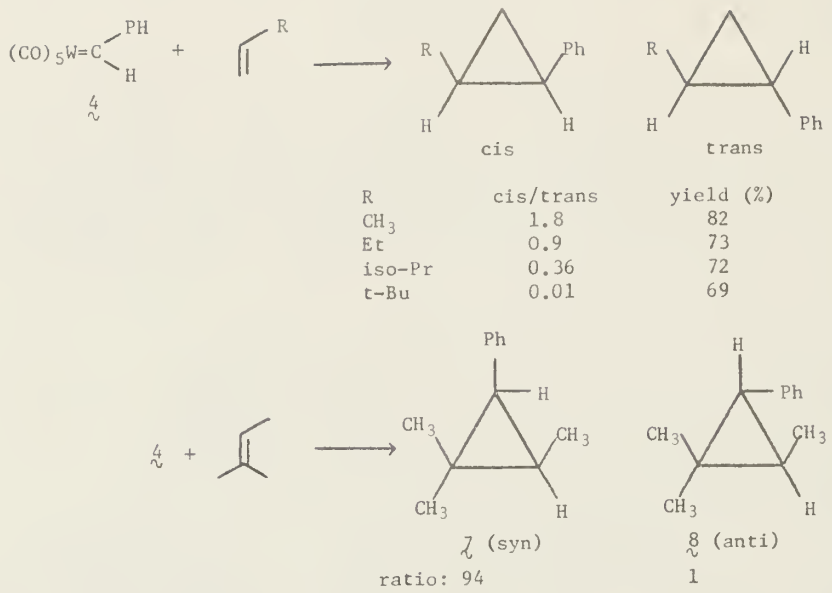
The mechanism of cyclopropane formation first proposed by C. P. Casey[11] in 1977 (as in Scheme IV) included a puckered metallacyclobutane intermediate.

Scheme IV



However, more detailed studies reported in this area ruled out this proposal. The metallocyclobutane mechanism fails to explain the smooth decrease in cis:trans ratio of cyclopropane formed from monosubstituted alkenes as the substituent becomes sterically larger. It further fails to explain highly selective formation of cis cyclopropane from 2-methyl-2-butene (Scheme V).

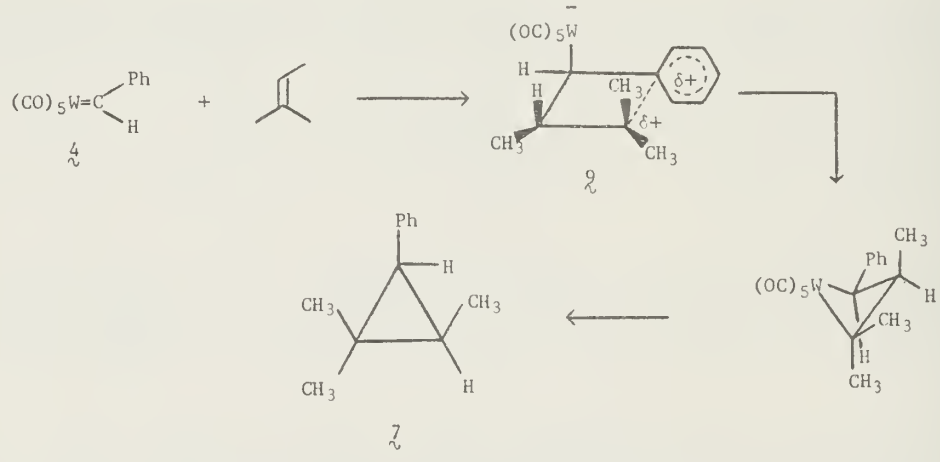
Scheme V



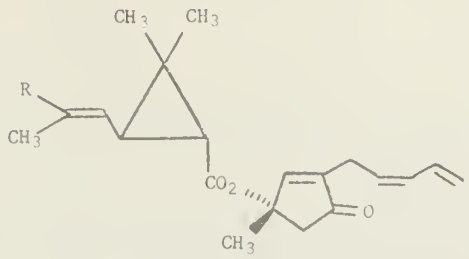
R	cis/trans	yield (%)
CH_3	1.8	82
Et	0.9	73
iso-Pr	0.36	72
t-Bu	0.01	69

In 1979, Casey proposed another mechanism that best explains the preferential formation of syn cyclopropanes proceeding through transition state 9 in which the positive charge developing on the more substituted carbon atom of the alkene is stabilized by donation of π-electrons from the benzene ring. Subsequent to the formation of 9, a metallacyclobutane intermediate may be formed.[8] The stereochemistry of the products is, however, determined at a transition state substantially early than the metallacyclobutane (Scheme VI).

Scheme VI



Functionally substituted cyclopropanes are widely distributed in nature.[23] Examples are well known in insecticides, such as the pyrenthrins,[23] and as intermediates[24,25] in the biosynthesis of steroids and carotenoids.[23] So the applications of metal-carbene complexes in the formation of cyclopropane rings are very important in organic or bioorganic synthesis.



R = CH_3 pyrethrin I
R = CO_2CH_3 pyrethrin II

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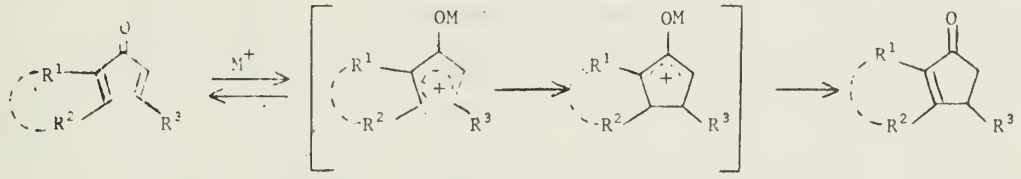
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SILICON DIRECTED NAZAROV CYCLIZATION

Reported by Todd Jones November 18, 1982

Interest in the total synthesis of cyclopentanoid natural products has spurred the development of many methods for the synthesis of cyclopentenones. The classical Nazarov[1] cyclization provides a general method for forming cyclopentenones as outlined in Scheme I. The mechanism proposed for a Nazarov cyclization is a conrotatory[2] ring closure of a pentadienyl cation to form an oxyallyl cation that loses a proton and tautomerizes to a cyclopentenone. Many variants of this reaction have been reported since Nazarov's pioneering work in the 1940's - 1950's.[3] These include a variety of methods to assemble a divinyl ketone[3], divinyl ketone equivalents[1,3k], and the use of lewis acids as catalysts.[3f,g]

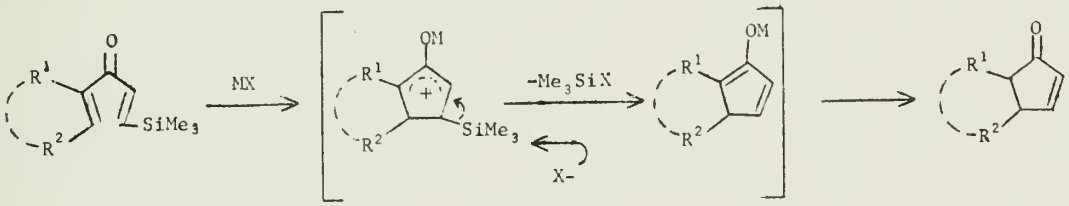
Scheme I.



A major limitation of all of these methods is lack of control over placement of the double bond in the cyclopentenone. The double bond normally resides in the thermodynamically most stable position. We have reported a new modification of the Nazarov cyclization that provides a solution to this problem and constitutes a general method for the preparation of 4,5-substituted 2-cyclopentenones.[4]

The key to this modification is the ability of silicon to control the regio - and stereochemical outcome of certain carbocation processes.[5] This effect, known as the β effect[6], has dominated the use of organosilicon chemistry in synthesis.[7] We reasoned that strategic placement of an organosilyl group as shown in Scheme II could direct the incipient double bond to the less substituted position.[8]

Scheme II.



A series of divinyl ketones have been prepared and cyclized with ferric chloride to yield cyclopentenones in yields from 27-99%. Stereochemistry of the substituents was secured by either direct equilibration or by hydrogenation to a saturated system followed by equilibration and comparison to known equilibrium ratios.[4]

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RECENT INVESTIGATIONS OF THE SILICON-CARBON AND SILICON-SILICON DOUBLE BOND

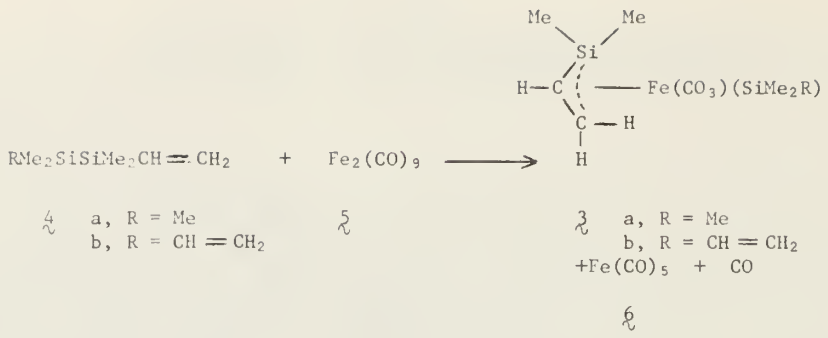
Reported by Dennis Sagl November 22, 1982

For years, silicon was thought to be incapable of forming stable $p\pi$-$p\pi$ multiple bonds to carbon or silicon. This was largely the result of an inability to isolate stable compounds of this type. Such species were found to exist only as transient intermediates, and various explanations such as poorer orbital overlap and the diffuse nature and high energy of silicon 3p orbitals were given to explain the instability of silicon π bonds to carbon or silicon.[1] Since the original work postulating the intermediacy of silaolefins[2] and disilenes[3] theoretical interest in these species has spurred experimental effort. Great strides have been made in the development of novel methods for the generation and spectroscopic characterization of transient silaolefins[4] and disilenes. Recent efforts have resulted in the synthesis of stable, isolable species containing these moieties.[5,6] An attempt will be made to review pertinent work leading up to and resulting in stable silaolefins and disilenes.

Silaolefin intermediates have been postulated in a number of reactions and have been generated by a variety of methods including cycloreversions, thermal rearrangements, and elimination reactions.[4] Trapping and labelling studies performed using these reactions provide a strong case for the intermediacy of silaolefins.

Further support for the existence of silaolefins comes from their low temperature matrix isolation and spectroscopic observation. The IR and UV spectra of 1,1,2-trimethyl-silaethylene, obtained by Chapman and by Schechter,[7b] provided the first physical characterization of a silaolefin. Since this initial work, spectroscopic studies of a number of silaolefins have been performed. Spectroscopic observation of 1-methylsilabenzene ($\underset{\sim}{1}$), which is generated by a thermally induced retro-ene reaction of 1-methyl-1-allylsilacyclohexa-2,4-diene ($\underset{\sim}{2}$),[8] provided some of the most convincing early evidence for the existence of transient silaolefins. Chapman and Barton have obtained the UV and IR spectra of $\underset{\sim}{1}$ isolated in an argon matrix at 23°K.[9] Comparison of the IR spectrum of the reaction products with spectra for $\underset{\sim}{2}$ and propene showed the presence of additional bands attributable to $\underset{\sim}{1}$. In addition, the UV spectrum of matrix isolated $\underset{\sim}{1}$ possessed absorption bands at much longer wavelengths than the spectrum of $\underset{\sim}{2}$ with well resolved vibrational structure. The appearance of the UV spectrum is similar to that observed for the $^1B_{2u} \longleftarrow {}^1A_{1g}$ transition of benzene. The bathochromic shift to the region around 310nm, from the 256nm region absorption observed for benzene, is in agreement with calculations obtained for silabenzene.[9] Bock and Barton have also obtained the photoelectron spectrum of $\underset{\sim}{1}$.[10] The observed first and second ionization potentials of 7.7 and 9.1 eV are comparable to the values of 7.8 and 9.15 eV expected from calculations.[10]

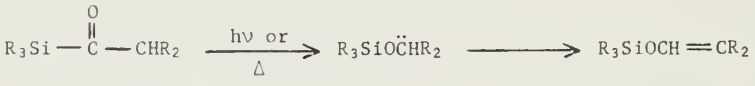
A stable metal complex postulated to have a silaolefin ligand was isolated by Sakurai and co-workers.[11] They utilized the stabilizing effect of a transition metal and attempted to isolate η^3-1-silapropenyl complexes of iron ($\underset{\sim}{3}$). Structure $\underset{\sim}{3}$ was tentatively assigned to the compounds isolated from the reaction of disilanes $\underset{\sim}{4}$ and nonacarbonyldiiron ($\underset{\sim}{5}$), based upon ^1H and ^{13}C NMR, IR,



4 5 3 6

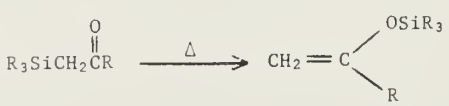
and mass spectra, as well as carbon and hydrogen elemental analysis. However, later investigations by McKennis[12,13], and ^{29}Si NMR studies by Sakurai[14] revealed that 3a is actually a η^2-tetracarbonyliron complex (7). Compound 7, isolated by McKennis, had a boiling point and refractive index similar to 3a. The spectra of 3a and 7 were in agreement, with the exception of the mass spectrum.[12] McKennis found a parent peak at m/e 326, which indicated the tetracarbonyl, 7, rather than the tricarbonyl, 3a, metal complex. The initial observation by Sakurai of a parent peak at m/e 298 and no peak at m/e 326[11] is understandable in view of the tendency for metal carbonyl complexes to lose carbon monoxide. In addition to the discoveries of McKennis, a ^{29}Si NMR study and a more careful determination of the mass spectrum of 3a by Sakurai[14] resulted in the conclusion that Sakurai's iron complex is indeed 7 rather than 3a. Later attempts by McKennis to generate η^3-silapropenyl iron complexes such as 3a from η^2-complexes such as 7 failed.[13]

The recent observations of relatively stable silaolefins[15], and the isolation of a stable, solid silaolefin[5] by Brook and co-workers is the result of a novel method for the generation of silaolefins which allows for the placement of different substituents on the double bond of the silaolefins. Brook had previously found that acylsilanes (8) rearrange to siloxycarbenes (9) either thermally or photochemically, and that 9 can give siloxyalkenes (10) by 1,2-



8 9 10

hydrogen migration[16]; furthermore, Brook had observed similar thermal rearrangements of β-ketosilanes (11) to siloxyalkenes (12).[17] Thus, the photolysis of acyldisilanes (13) to produce disiloxycarbenes (14) and/or sila-



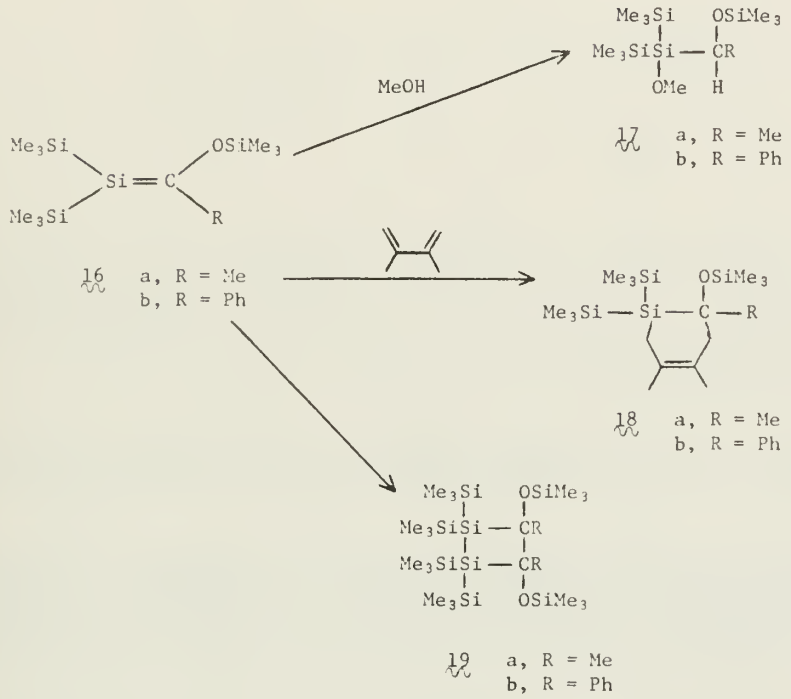
11 12

olefins (15) was not unexpected.[15a] Evidence for the formation of 16 includes isolation of the dimer (19), as well as products resulting from trapping with



13 14 15

methanol (17) and 1,3-dimethylbutadiene (18). Later studies on the mechanism of photolytic rearrangements of acyldisilanes[15b] resulted in the discovery of



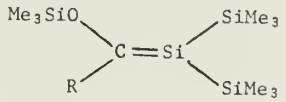
16 a, R = Me
b, R = Ph

17 a, R = Me
b, R = Ph

18 a, R = Me
b, R = Ph

19 a, R = Me
b, R = Ph

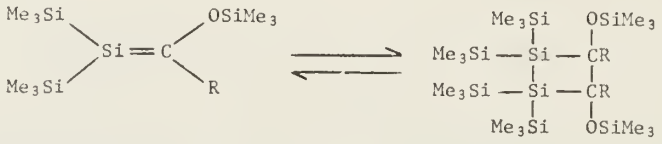
a very stable silaolefin (20a). Compound 20a, which was stable for 2 weeks in an NMR tube, was found to be in equilibrium with the starting acyldisilane and its dimer. Evidence for the existence of 20a in solution includes ^{1}H, ^{13}C, and preliminary ^{29}Si NMR spectra as well as UV and IR spectra.[15b] The presence of a signal at 212.7ppm below TMS in the ^{13}C NMR spectrum, and the presence of a signal at 41.2ppm downfield from TMS in the ^{29}Si NMR spectrum are especially striking. Later, more definitive ^{29}Si NMR studies[13c,d] on 20a,



20 a, R = t-butyl
b, R = $CE+_3$
c, R = 1-adamantyl

20b, and 20c, in addition to a series of reference compounds, indicated that the ^{29}Si signal found in the range 40 to 55ppm downfield from TMS is probably due to an sp^2hybridized silicon. In addition, the increase in the coupling constant between the $p\pi$-$p\pi$ bonded carbon and silicon to 84 Hz, significantly larger than the 64-70 Hz range found for carbon-silicon coupling through a single bond, is further evidence for the double bond. Compound 20c was later isolated as a solid and characterized by ^{1}H, ^{13}C, and ^{29}Si NMR, IR, and mass

spectra to give further data consistent with a carbon-silicon double bond[5a]; however, the most convincing evidence for the carbon-silicon double bond in 20c is the bond length of 1.764 Å, as determined by X-ray diffraction at -50°C. This distance is considerably shorter than normal 1.87-1.91 Å length of a carbon-silicon single bond. Other studies by Brook and co-workers[18] probed the factors which influence the stability of the carbon-silicon double bond. It was found that for compounds such as 21, a substituent such as a substituted or unsubstituted phenyl group or a trifluoromethyl group did not stabilize 21

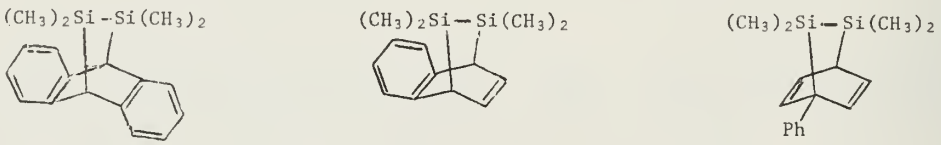


21 22

relative to the dimer, 22, while t-butyl, 1-adamantyl, or 1-(1,1-diethyl)-propyl groups did so.[18] This would tend to indicate that conjugative interactions with aromatic π systems or the electron-withdrawing inductive effect of a trifluoromethyl substituent are less important than steric bulk in the stabilization of silaolefins.

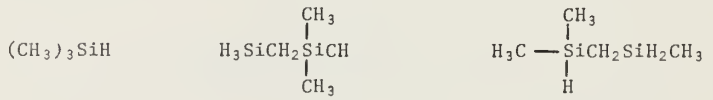
Although not as extensively studied as silaolefins, disilenes, compounds containing a silicon-silicon double bond, have still been of interest to researchers.

A disilene was first postulated by Roark and Peddle[3] in the thermal decomposition of various 7,8-disilabicyclo[2.2.2]octa-2,5-dienes (23, 24, 25) at 500, 360, and 260°C respectively. Low pressure pyrolysis of 24 and 25 and con-

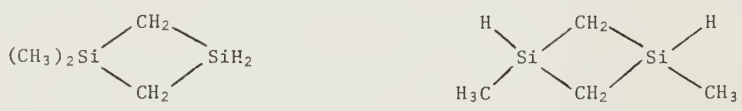


23 24 25

densation of the products in a liquid nitrogen trap yielded the respective aromatic hydrocarbons, a trace of trimethylsilane, and a nonvolatile viscous white oil. When the trap was allowed to warm, volatile products were condensed in another liquid nitrogen trap. Analysis of the product mixture showed it to consist of 26 (3%), 27 (0.5%), 28 (2%), 29 (30%), and 30 (10%). The major products, 29 and 30, were rationalized to arise by a mechanism involving the



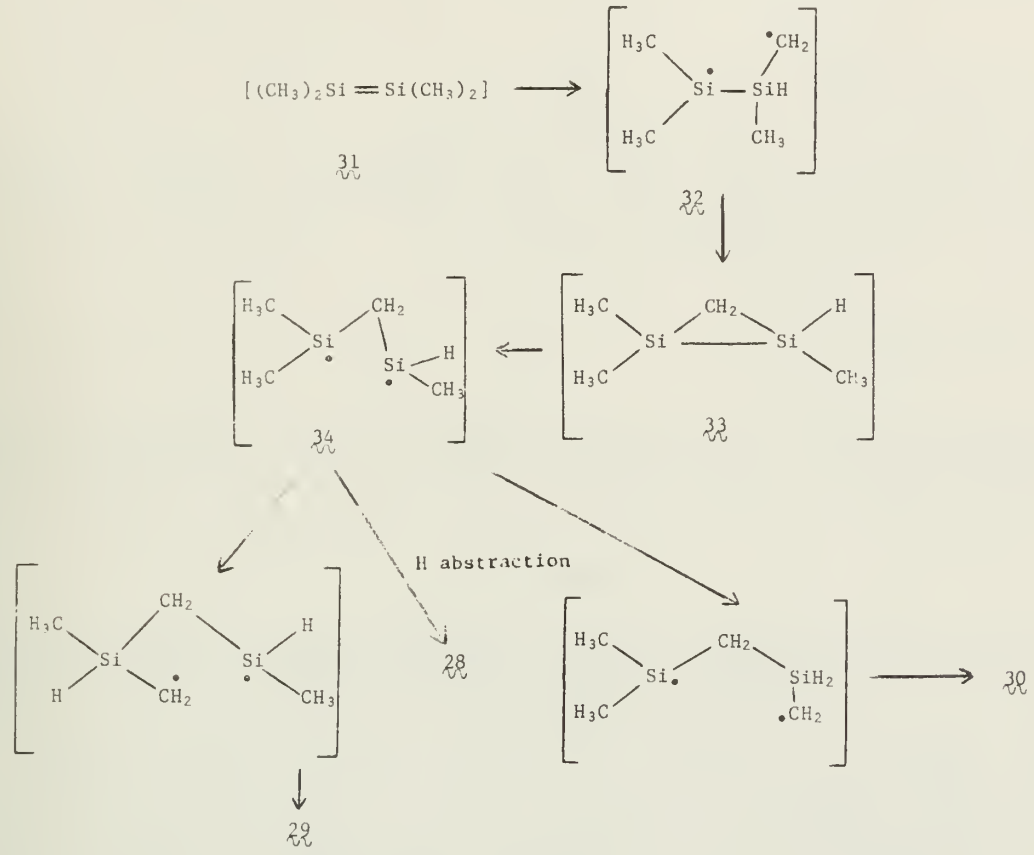
26 27 28



29 30

disilene 31. Although the exact nature of this mechanism (Scheme I) has been questioned, the initial formation of a disilene is generally agreed upon, as alternative mechanisms postulate the rearrangement of the initial disilene to

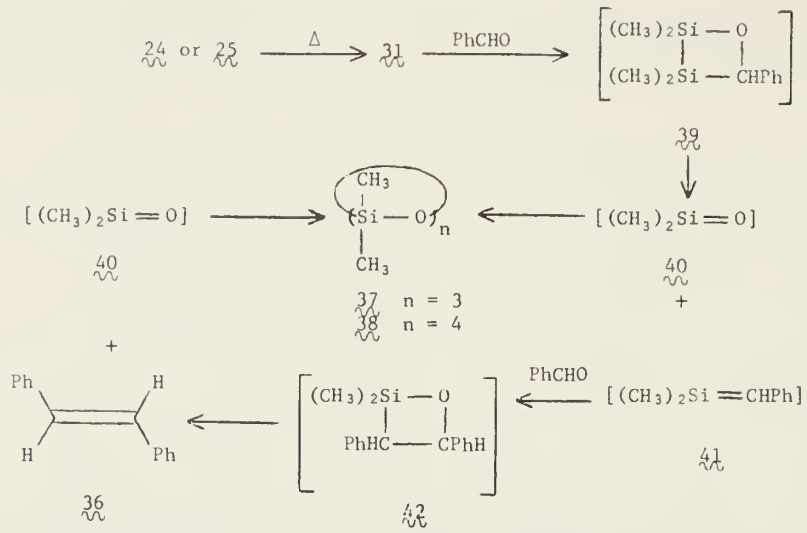
Scheme I.



a silylene.[19] In order to obtain more direct evidence for the initial formation of 31, the intermediate was trapped via Diels-Alder reactions. When 23 was pyrolyzed in the presence of 9-deuterioanthracene (35), exchange of 31 occured to give a statistical mixture of monodeuterated and undeuterated 23. Both 24 and 25 reacted thermally in the presence of anthracene to give virtually quantitative yields of 23, and 25 reacted with naphthalene to give a quantitative yield of 24. In addition, pyrolysis of 25 in the presence of a 2,3-dimethylbutadiene gave the Diels-Alder product in 29% yield.

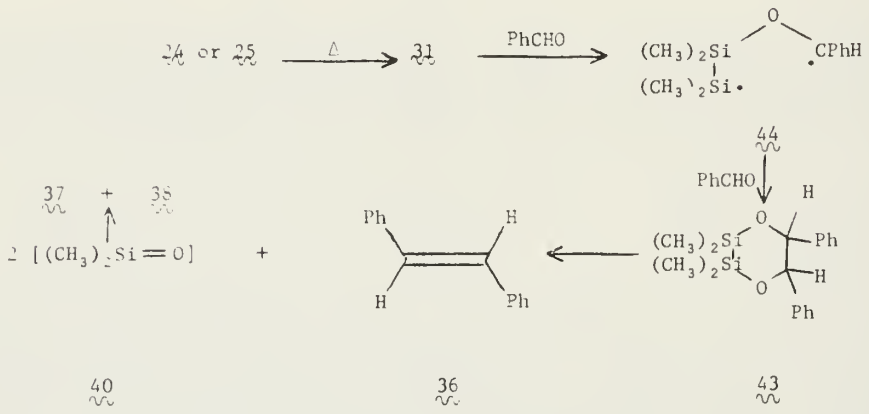
Later investigations by Barton and Kilgour[20,21] showed 24 or 25, when heated to 500°C in the presence of a 20:1 excess of benzaldehyde, to produce naphthalene or biphenyl along with trans-stilbene (36) and a mixture of siloxanes 37 and 38. The reaction was proposed to involve 31 as an intermediate in the mechanism (Scheme II). Pyrolysis of neat benzaldehyde, or the pyrolysis of well established generators of dimethylsilylene in the presence of bezaldehyde, under similar conditions failed to yield the product mixture observed from the pyrolysis of 24 or 25, but pyrolysis of 2,3-disila-1,4-dioxane (43) gave 19 (73%), 37 (28%), and 38 (17%). Thus, a second mechanism (Scheme III) could not be ruled out; however, this mechanism also involved disilene 31 as an intermediate.

Scheme II.

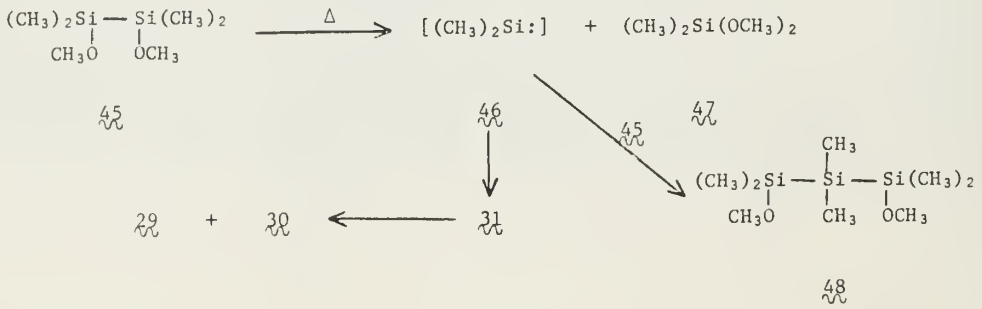


Gaspar and Conlin have presented evidence for the generation of disilenes by another route.[22] Flow pyrolysis of 1,2-dimethoxy-1,1,2,2-tetramethyldisilane

Scheme III.

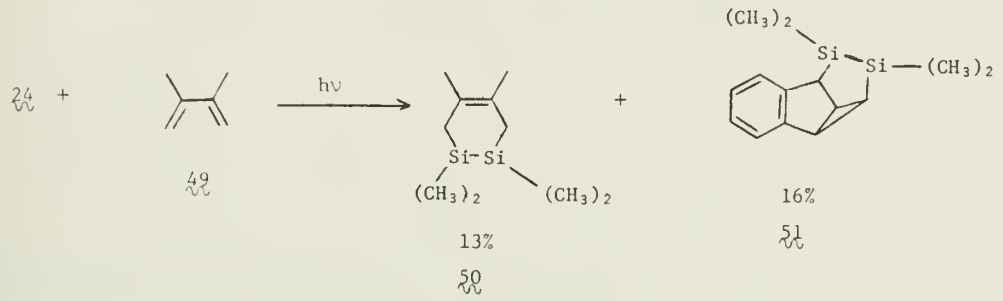


(45), a known generator of dimethylsilylene (46),[23] resulted in formation in 14% yield of 48, the product expected from attack of 46 on 45; however, three disilacyclobutanes are also obtained in 28% total yield. The two formed in greatest yield, 29 and 30, had been previously characterized as the major products resulting from formation of 31,[3] suggesting the possibility of 31 as a common intermediate. Copyrolysis of 45 with excess propyne, used as a silylene trap, gave further evidence for the initial generation of 46. In addition, the ratio of 29 and 30 to 46 trapped as products increases as the pyr-



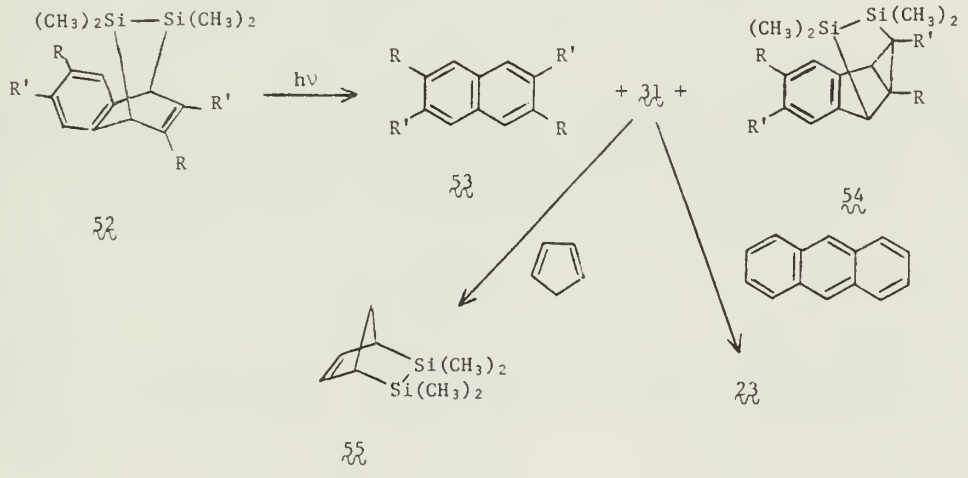
olysis temperature is increased from 600 to 700°C. This result is consistent with the increasing propensity of 46 to undergo bimolecular reactions due to the increased concentration of 46 at higher temperatures. The generation of disilenes from silylenes was given further credence by Sakurai and co-workers.[24] Silylenes generated by pyrolysis of variously substituted methoxysilanes or 7-silanorbornadienes were shown to give 23 when pyrolysis was carried out in the presence of anthracene.

Although the thermolytic formation of disilenes has been known for some time,[3] strong evidence for the photolytic generation of disilenes has only recently been obtained.[25,26] Photolysis of 24 in the presence of the butadiene, 49, gave a 13% yield of the Diels-Alder adduct (50), along with a 16% yield of an isomeric product (51).[25] The trapping of 31, generated photolytically from

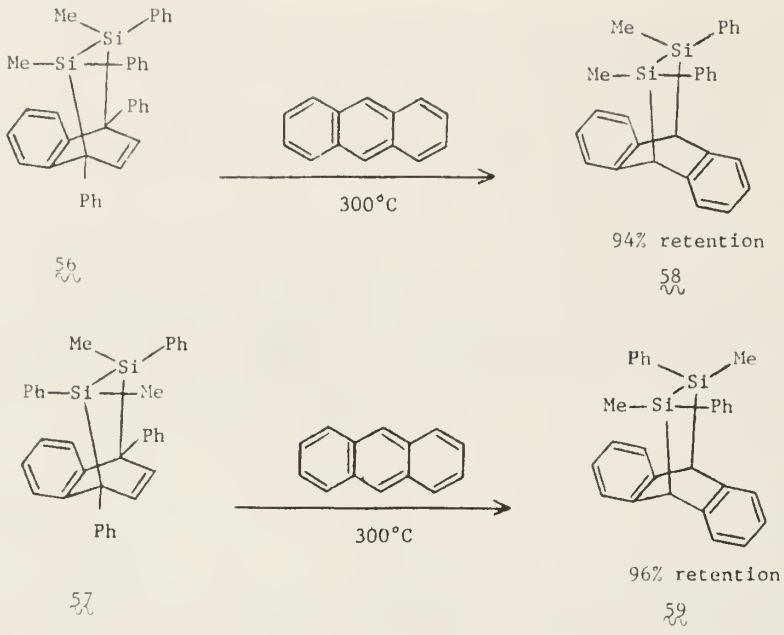


variously substituted adducts of 52, by anthracene and cyclopentadiene supplies further evidence for the photolytic generation of 31.[26]

The double bond character of disilenes, evidenced in hindered rotation about the silicon-silicon bond, was demonstrated by Sakurai in the pyrolysis of cis and trans-2,3-benzo-1,4,7,8-tetraphenyl-7,8-disilabicyclo[2.2.2]octadiene (56 and 57).[27] Trapping of the resulting disilenes with anthracene gave at least 90% retention of configuration in all cases.



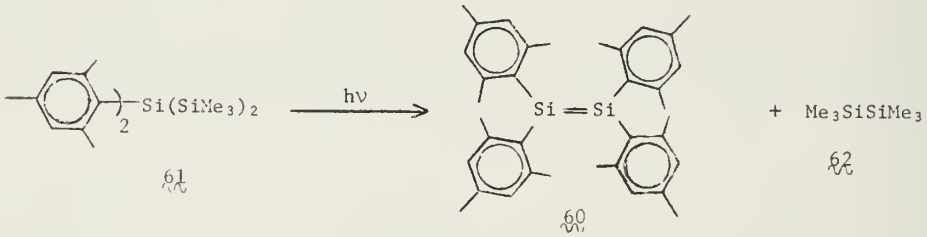
The synthesis of stable disilenes has only recently been achieved,[6] by utilization of the concept that the steric bulk of substituents would stabilize a disilene. West and co-workers[6a] isolated what was postulated to be tetramesityldisilane (60) from the photolysis of 2,2-bis(mesityl)hexamethyltrisilane (61) in hexane or 3-methylpentane at -100°C. The ^{1}H, ^{13}C, and ^{29}Si NMR, IR, UV,



56 58

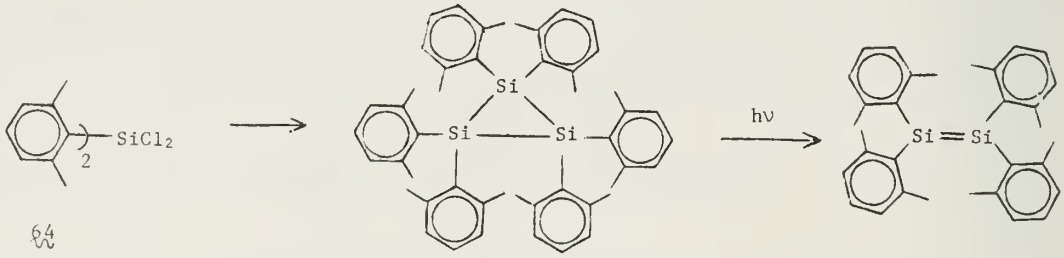
57 59

and mass spectra, as well as elemental analysis support the postulated structure The presence of a parent ion at m/e 532, a ^{29}Si NMR signal at 63.9ppm downfiled from TMS, and a UV transition at 420nm, assigned to the first $\pi \rightarrow \pi^*$ transition, are among the better pieces of supporting evidence for structure 60. It was further shown that 60, stable at room temperature in the absence of oxygen, underwent addition reactions similar to olefins with HCl, ethanol, and O_2 to give the substitution products. Almost concurrently, Masamune and co-workers[6b] syn-



61 60 62

thesized the stable tetra-(2,6-dimethylphenyl)disilene (62) from the photolysis of 63. Like 60, 62 is air and moisture sensitive, and reacts with bromine to give 65. Although not as well characterized as 60, the structure of 62 is supported by its ^1H NMR, UV, and high resolution mass spectra.



64 63 62

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RECENT SYNTHETIC APPROACHES TO DODECAHEDRANE[1]

Reported by James E. Hunter November 29, 1982

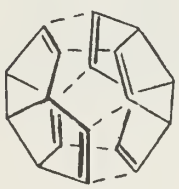
Compounds with carbon skeletons corresponding to the regular polyhedra have been a target of synthetic chemists for a number of years.[2] Eaton in 1964 synthesized the first such compound, the square-faced polyhedron cubane.[3] With the successful synthesis of t-butyltetrahedrane in 1978[4], dodecahedrane remained the lone regular polyhedron whose skeleton could be constructed with tetrahedral carbons.

The interest in dodecahedrane goes beyond the challenge of building the highly symmetrical framework. Numerous, sometimes conflicting theoretical calculations of dodecahedrane's structural parameters and spectral properties have been made and await verification.[5-11] For example, the calculated heat of formation obtained using molecular mechanical methods vary from 45.8[5a] to -0.22[6] kcal/mole, while molecular orbital calculations at MINDO/3 and STO-3G levels give values of 80.1[9] and -29.4[11] kcal/mole, respectively. Calculations on the stability of inclusion compounds, in which an atom or ion occupies the central cavity have been made with STO-3G and PRDDO molecular orbital methods. The results suggest that a H^+ or Be^{++} cation in the central cavity would be thermodynamically more stable relative to infinite separation. Practical applications have also been suggested for dodecahedrane. The high symmetry and rigidity expected for dodecahedrane and its derivatives make them desirable model compounds for physical organic studies.[8] Dodecahedrane, like other polycylic hydrocarbons, may be pharmaceutically useful as carriers of biologically active compounds.[2] It has been speculated that the lipophilicity of thes compounds allows for more efficient transport to the active site.[12]

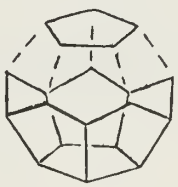
Synthetic Approaches

The task of constructing the dodecahedrane framework is a formidable one. Twelve cyclopentane units must be fused in an all cis fashion resulting in a compound of high torsional strain from the twenty eclipsed methine protons. The predicted C-C-C bond angle of 108° and C-C-H angle of 110°54', for a dodecahedrane molecule of I_h symmetry, differs only slightly from the bond angle of an idealized tetrahedrane (109°28'). Bond angle strain therefore, is only a minor contributor to the total strain of the molecule.

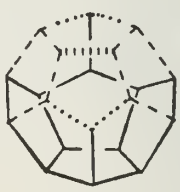
The synthesis requires that at some point severe steric interactions must be overcome as the concave units are brought together. Many different approach have been tried, but only three of the more thoroughly explored ones will be discussed. Dodecahedrane's synthesis can be envisioned through dimerization 1, a capping process 2, or through a symmetrical knitting scheme 3, which was successfully employed by Paquette.[13]



1



2

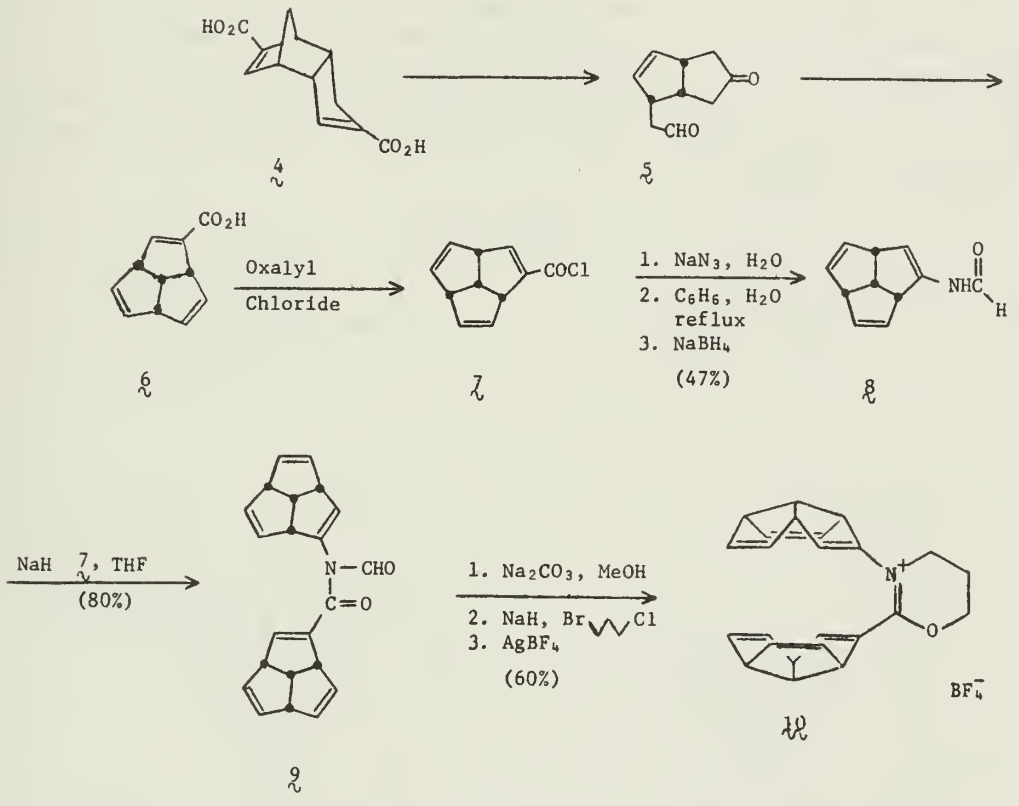


3

Dimerization. Woodward was among the first to realize that conceptually dodecahedrane is nothing more than dimerized triquinacene.[14] All attempts to synthesize dodecahedrane in this manner have failed, however, presumably because of the unfavorable entropy of activation and the steric interactions of the olefinic protons involved in attaining the appropriate transition state. Recent efforts have focussed on physically constraining the triquinacene units in such a manner that the appropriate methine carbons of each monomer may be brought into close proximity.

Deslongchamps' approach was to restrict the motion of the triquinacene units using an imidate bridge, as in compound 10.[15] His triquinacene monomer is derived by conversion of readily available Thiele's acid 4[16] to aldehyde 5, with sodium azide under acidic conditions, followed by photolysis. An aldol condensation leads to a hydrocarbon in which all the methine hydrogens are on the same face.[17] Further elaboration gives the racemic triquinacene-2-carboylic acid 6. This is obtained as the pure (+)-enantiomer after derivitization with (-)-quinine and recrystallization. After coupling, the triquinacene units are locked in a stacked orientation by cyclization and conversion of the carboxamide to the imidate salt. Rotation is still possible about the triquinacene-imidate bond, so that a face to face orientation is not guaranteed. Attempted coupling by thermolysis, photolysis or by electrochemical means were not successful.

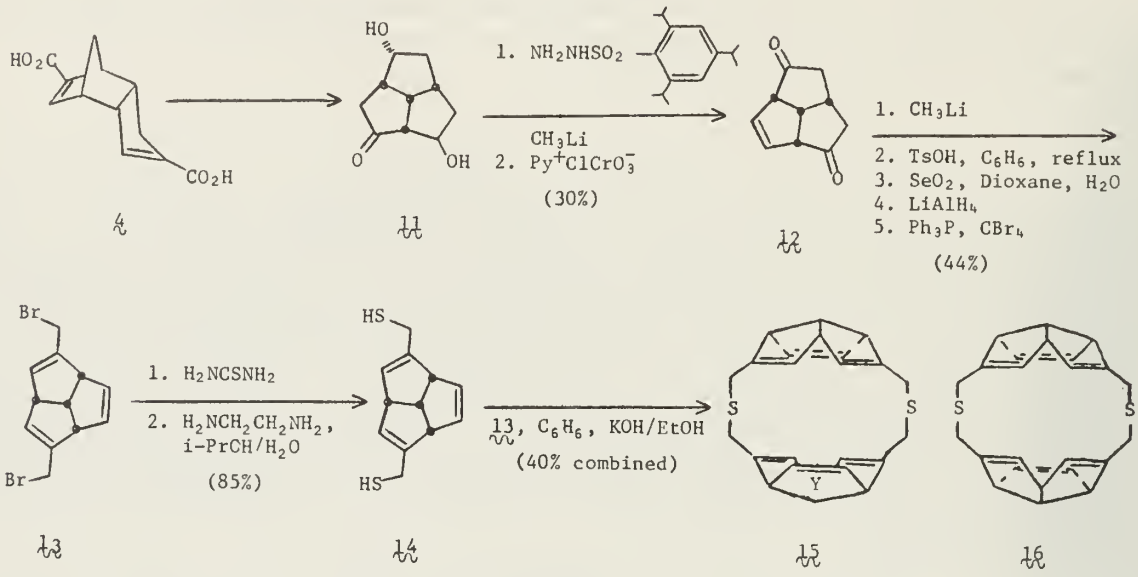
Scheme I



Following a procedure analogous to those developed in the synthesis of cyclophanes, Roberts has prepared the anti-dithia[3,3](2,6)-triquinacenophane 15.[18] Roberts synthesis is shown in scheme II. This approach has the advantage that enantiomerically pure starting materials are not required and the diastereomeric products are easily separated by crystallization. Thus, 15 is obtained in a three to one excess over the syn-isomer 16. The X-ray structure

of 15 shows that the two triquinacene units are properly disposed in an approximate dodecahedrane configuration. Successful completion of this synthesis has not yet been reported.

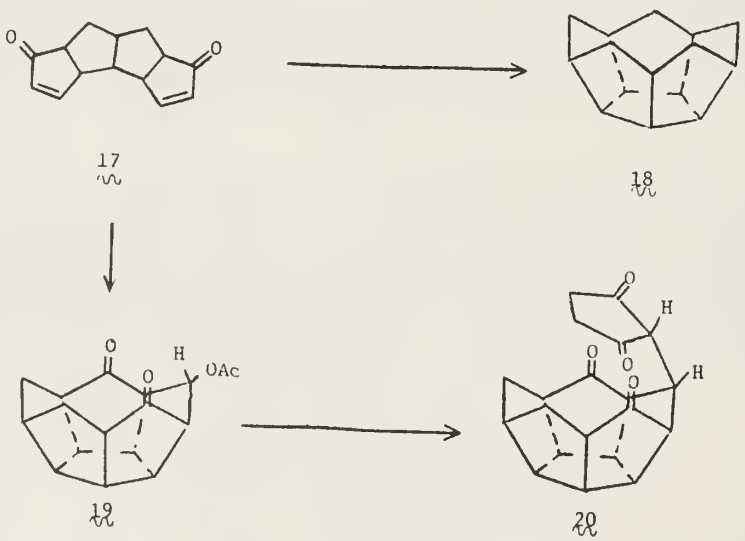
Scheme II



4 11 12 13 14 15 16

Capping. The coupling of cyclopentane and pentaquinane derivatives has so far proven to be unsuccessful. Eaton, who developed the synthetic route to peristylane 18,[19a] has been actively pursuing this approach. Most noteworthy is that he finds it feasible to construct his hemispherical pentaquinane framework late in the synthetic scheme by the cyclization of the four linearly fused cyclopentane rings 17. To date, Eaton has reported compounds in which a linkage between only one carbon of a substituted peristylane and cyclopentane-1,3-dione has been formed.[19b]

Scheme III

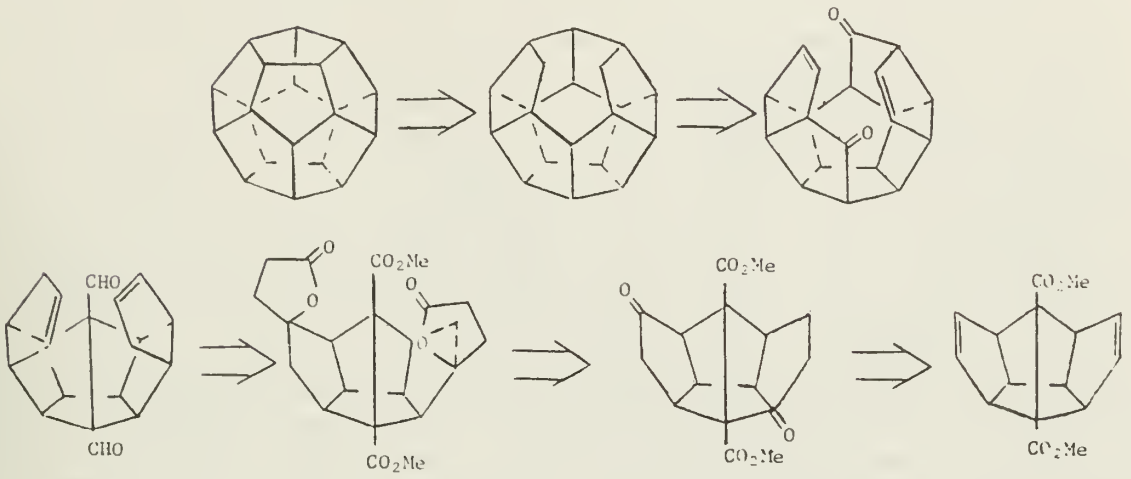


17 18 19 20

Symmetrical Knitting. The synthesis of dodecahedrane has recently been completed by Paquette and coworkers. The retrosynthetic analysis of the synthetic problem is summarized in scheme IV. This approach takes advantage of the high degree of symmetry inherent in the molecule to simultaneously form those bonds which are related to each other by C_2 symmetry. To accomplish this it is necessary to use intermediates which are functionalized with C_2

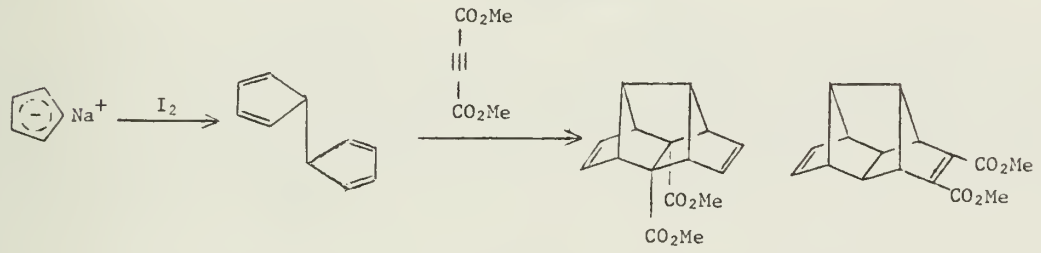
symmetry. It was hoped that the two reactive sites would not effect each other so that the transformations would occur with the same regio- and

Scheme IV

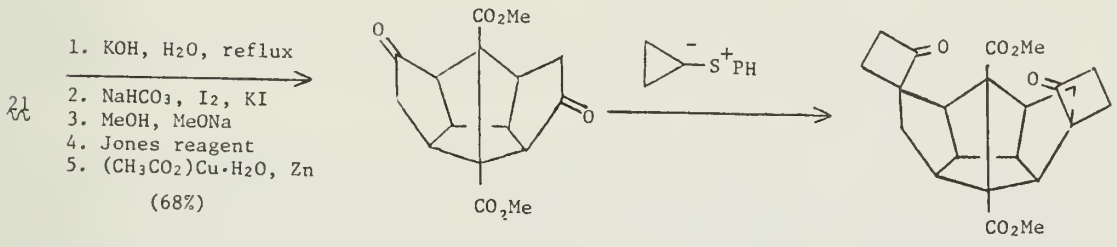


stereochemistry. This minimizes the number of steps required and permits ^{13}C NMR spectra to be used very efficiently for structure elucidation if axial symmetry is maintained.

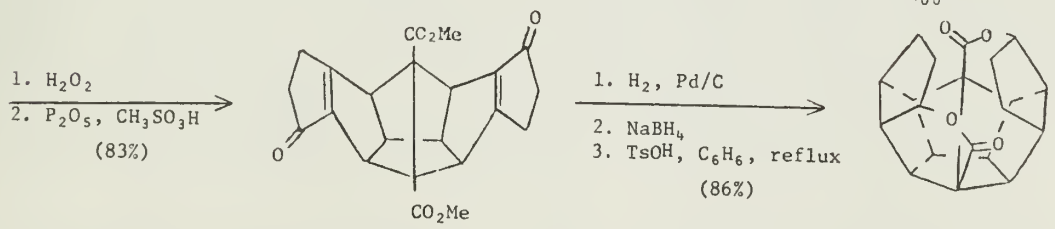
Scheme V



21 22



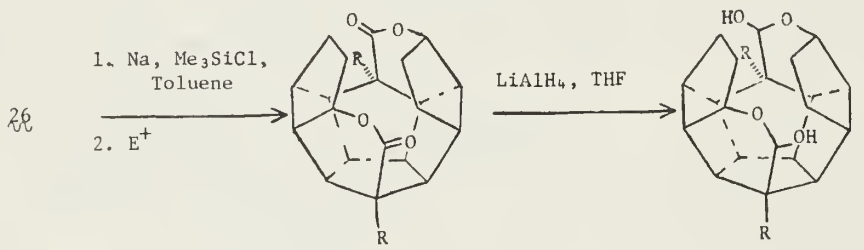
21 23 24



25 26

The ultimate precursor in this symmetrical knitting process is the fused norborenyl derivative 21. This diester possesses four of the twelve cis fused cyclopentane rings required and its functionalities are disposed with the proper C_2 symmetry. Compounds 21 and 22 are conveniently synthesized from dimethyl acetylenedicarboxylate and 9,10-dihydrofulvalene[20], derived from sodium cyclopentadiene and iodine. Two major isomers result from the Diels Alder reaction. The desired isomer is formed when the acetylene approaches the diene from the face in which the cyclopentadiene is bridged. Isomer 22, formed by initial cyclization at the outer face, can be separated by selective saponification. The more hindered diester 21 is then hydrolyzed under more vigorous conditions. Many methods may be envisioned to obtain the cross corner ketone 23, but iodolactonization, followed by esterification, Jones oxidation and the reductive cleavage of iodine provides for the formation of only the C_2-isomer. Ketone 23 is converted to a mixture of spiro-cyclobutyl-ketones by Trost's diphenylsulfonium cyclopropylylide[21] which is formed reversibly from the tetrafluoroborate salt and potassium hydroxide. Ketone 23, however, is sensitive to strongly basic conditions. It is necessary then, to use large excesses of the salt to shift the equilibrium sufficiently towards the ylide. The lactone derived from 24 is recovered as the dominate product after recrystallization of the Baeyer-Villiger reaction mixture. Reduction of 25 produces a highly spherical intermediate in which solvents as well as reagents should be impeded, if not prohibited from entering the cavity. Now, major problems in controlling the stereochemistry are not expected since the approach of reagents are restricted to the outer face.[22]

Scheme VI



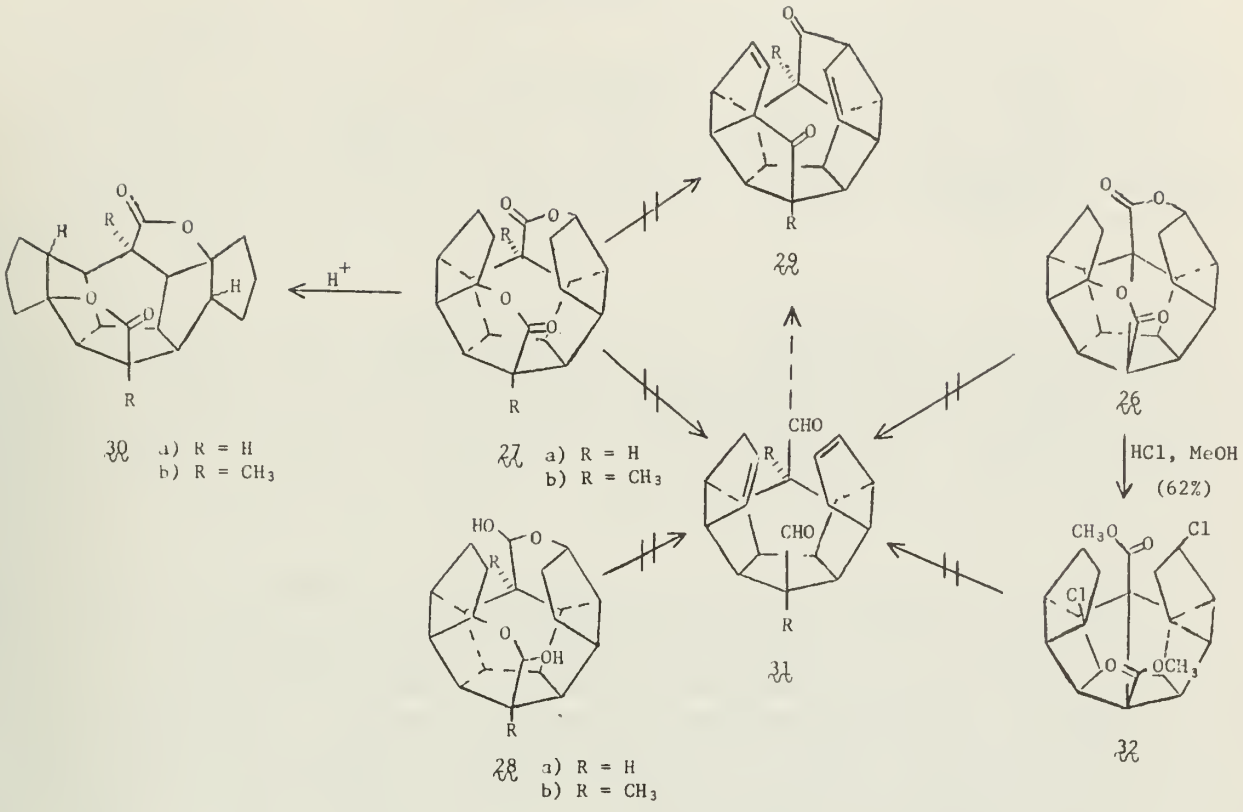
27 a) R = H
b) R = CH

28 a) R = H
b) R = CH_3

At this point the internal bond can be cleaved and the ensuing dilactone 27a reduced to the hemiacetal 28a.

The plan next called for dehydrative ring contraction for which 26, 27a, and 28a were all attractive intermediates. Paquette attempted to directly convert 27a to 29 under the strongly acidic conditions used to synthesize 25. Treatment with methanesulfonic acid and phoshporus pentoxide, however, afforded 30. The strain relieving isomerization of the cyclopentane rings is observed in other instances when forcing conditions are used. Paquette then turned his attention to the formation of the unsaturated aldehyde 31. This can conceivably be transformed to 29 by an intramolecular Prins reaction. Compounds 27a and 28a proved to be unsatisfactory precursors to 31. Both are especially susceptible to transannular bonding between the enolizable center on one side and its carbonyl counterpart on the other. Transannular reactions still predominated in 28b, in which the enolizable centers are blocked. Efforts to reach 29 through other derivatives of 27a and 28a eventually succumbed to facile reactions across the unsolvated cavity.[23]

Scheme VII



30 a) R = H
b) R = CH_3

27 a) R = H
b) R = CH_3

28 a) R = H
b) R = CH_3

29

26

31

32

Attempts to convert 26, which is immune to further transannular reactions, to 31 suffered from the inability to open both lactone rings. Presumably, strain-relieving conformational changes upon opening of the first lactone ring distorts the molecule in such a way as to make the second lactone very unreactive. An exception though, is reported for the reaction of 26 with methanolic hydrogen chloride to give 32.

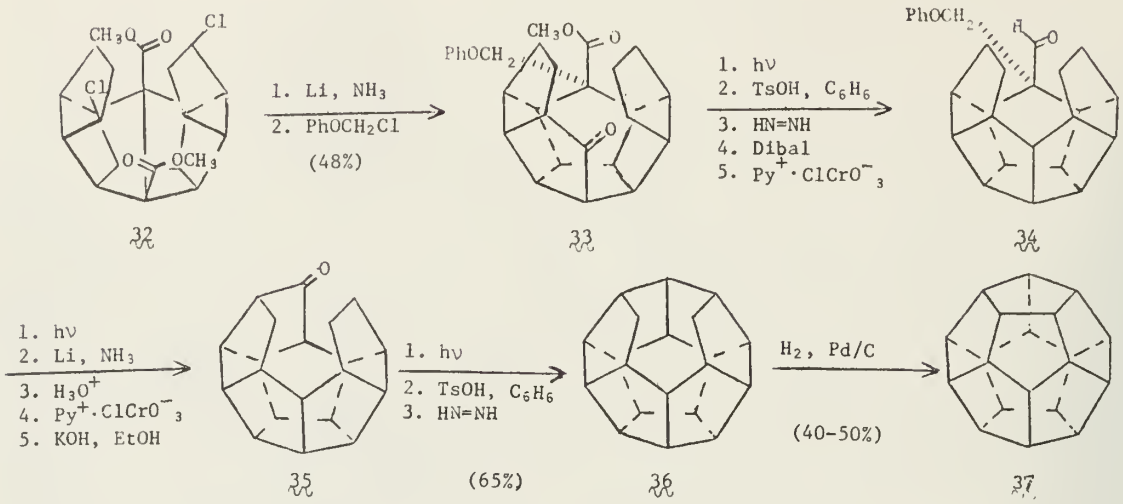
Attempts to dehydrochlorinate 32 and form an olefin analogous to 31 under basic conditions failed. It was found that the chloride could be eliminated with the radical anion generated in a Birch reduction. The internal bond and the other chlorine substituent are concurrently removed. The resulting compound has lost C_2 symmetry and with it the efficiency of carrying out two transactions at once.

It is necessary to quench the Birch reaction mixture with an electrophile capable of blocking the newly created enolizable centers. This prevents transannular bond formation. The degree of methylation can be controlled so that the dominant products has one to three methyl substituents. Elaboration of the mono and dimethyl derivatives ultimately leads to methyl-[24] and 1,16-dimethyldodecahedrane.[25] Paquette, seeking unsubstituted dodecahedrane, was in need of a protecting group which could be introduced after the Birch reduction and which would be inert to the ensuing photochemical reactions devised for the substituted systems. Phenoxymethyl met these requirements and was introduced as the chloromethylphenyl ether.

Solid state photochemical studies by Scheffer and Dzakpasu [26] indicated that intramolecular hydrogen abstraction was possible when the carbonyl oxygen was as far away as 2.2 to 2.5 Å from the proton. A further requirement was

that the C-H bond must be nearly in the plane of the carbonyl. Models in-

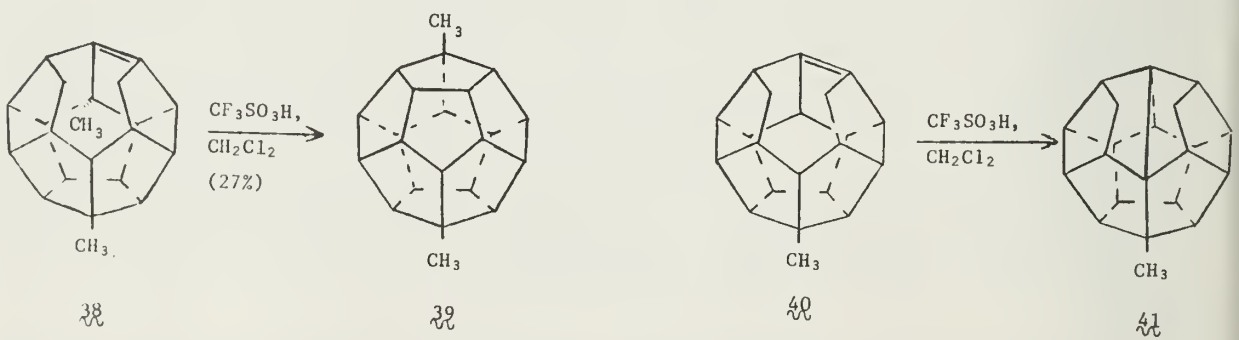
Scheme VIII



dicated that 33 might meet these requirements and indeed δ-hydrogen abstraction and 1,5-carbon bond formation did occur upon irradiation. The synthesis is completed in an iterative process. A carbon-carbon bond is formed by a Norrish type II photoreaction. This is followed by functional group manipulations to generate another photoreactive carbonyl. Relatively high yields are maintained, except for the Norrish reaction involving aldehyde 34. It suffers from photo-induced decarbonylation. The protecting group is converted to an aldehyde and cleaved in a retro aldol condensation. The final bond is achieved by dehydrogenation of hydrocarbon 36 over palladium. This method is also used to join the last two carbons in the synthesis of the monomethyl derivative.

The final bond in the 1,16-dimethyldodecahedrane synthesis is achieved under acidic conditions. Treatment of 38 with trifluoromethanesulfonic acid yields numerous products. The major constituent is compound 39, in which final bond formation is accompanied by a 1,2-methyl shift. Attempts to repeat this transformation with the monomethyl derivative fails to give a dodecahedrane product, rather transannulary bonded 41 results. At this time it is not known if the 1,2-shift occurs prior to or after the dodecahedrane framework is formed.

Scheme IX



Physical Properties

Dodecahedrane, as well as the mono- and dimethyl derivatives, forms colorless crystals which do not melt in a sealed capillary tube upon heating to temperatures as high as 420°C. 1,16-Dimethyldodecahedrane, the most studied compound of the three, shows three resonances in the ^{1}H NMR at δ=3.44 (12H), 2.94 (6H), and 1.19 (6H)ppm.[25] These chemical shifts correspond to the resonances observed in the monomethyl derivative of δ=3.38 (br, 16H), 2.98 (3H), 1.14 (3H)ppm.[24] The inner cavity of the dimethyl derivative has a diameter of 0.9 Å, when allowances are made for the Van der Waals radius of carbon.[27] This is large enough to accommodate Be^{++} which has a Pauling crystal radius of 4.4 Å.

Dodecahedrane, as expected, exhibits only one ^{1}H NMR and ^{13}C NMR resonance at δ-3.38 and 66.93ppm, respectively.[13] The observed carbon-hydrogen coupling of 134.9 Hz corresponds to 27.0% s character or $sp^{2.7}$ hybridization. Schulman's value based on semiempirical calculations has J_{C-H} equal to 125.3 Hz.[9] A comparison of the infrared and Raman active bands observed to those calculated by Ermer[7] are given in Table I and II. Ermer's theoretical values are found using Constant Force Field Calculations and are in rough agreement with those observed.

Table I

Frequencies of Dodecahedrane's Infrared Active Bands

Theoretical (cm^{-1})	Observed (cm^{-1})
2898	2945
1310	1298
760	728

Table II

Frequencies of Dodecahedrane's Raman Active Bands

Theoretical (cm^{-1})	Observed (cm^{-1})
2899	2945
2895	2938
1300	1324
1166	1162
1101	1092
846	840
732	676
395	480

Summary

Now that the synthesis of dodecahedrane has been completed, some of the questions concerning this novel compound's properties and potential uses cited earlier, may be addressed. Further investigation is warrented into the mechanism of the final transformation in the 1,16-dimethyldodecahedrane synthesis and into some of the transannular reactions. Work to further modify dodecahedrane and into substituting heteroatoms into the carbon framework are underway and should be of considerable interest.

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STEREOELECTRONIC CONTROL IN TETRAHEDRAL INTERMEDIATES

Reported by Burney Lee December 2, 1982

It is generally accepted that the hydrolysis reactions of amines, esters, imidate salts, and orthoesters proceed through a tetrahedral intermediate.[1] In 1975, Deslongchamps postulated that the precise conformation of the tetrahedral intermediate is transmitted into the products of the reaction and that the specific decomposition of an intermediate is controlled by the orientation of the lone pair orbitals of the heteroatoms. He defined stereoelectronic assisted cleavage of a tetrahedral intermediate in the following way: specific cleavage of a carbon-heteroatom bond occurs when two heteroatoms of the tetrahedral intermediate each have a lone pair orbital oriented antiperiplanar (app) to the departing heteroatom-alkyl group. In those cases where the initially formed tetrahedral conformer cannot undergo stereoelectronically assisted bond cleavage, it is proposed that conformational changes become more facile than unassisted cleavage and new conformers must be considered. This does not mean that unassisted cleavage cannot occur but that it is considered a higher energy process. The effect and scope of stereoelectronic control in the decomposition of tetrahedral intermediates of the categories mentioned above is considered in this paper.

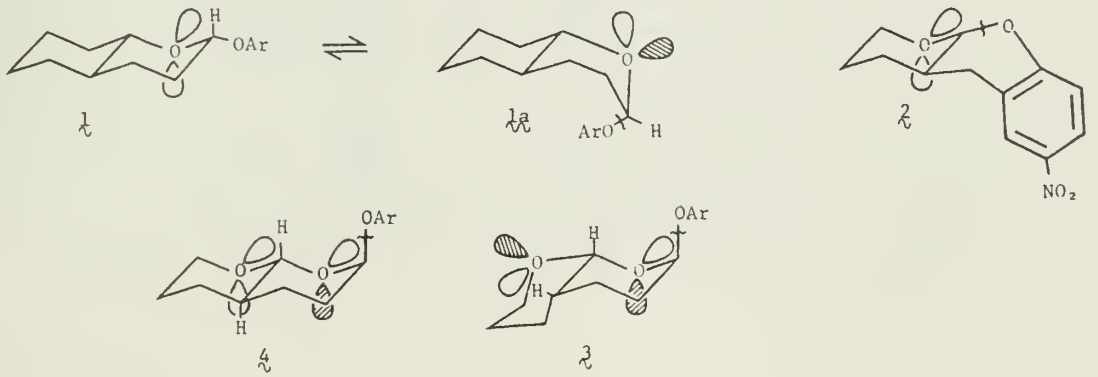
The tetrahedral intermediate lone pair geometries are discussed in terms of the simple sp^3 hybrid picture of the heteroatoms involved. This simple approach agrees with the more sophisticated HOMO-LUMO picture where the HOMO lone pair p orbital of an oxygen atom involved in stereoelectronic control contributes electron density to the cleaving bonds LUMO orbital, σ^*, thereby weakening that bond and concurrently strengthening its own bond to the central atom by imparting double bond character to it. MO calculations indicate the σ^* donation is possible when the dihedral angle, R-C-Y-R, Y=heteroatom, R=H, alkyl, is 150° or 300°, a situation amenable to a sp^3 model.[2] The transition state should resemble the tetrahedral intermediate and for simplicity the latter is used to describe stereoelectronic effects.

Stereoelectronic control in acetals

Although no tetrahedral intermediate is formed in the reactions of acetals, a conformation dependence on their reactivity and stereospecificity is seen.

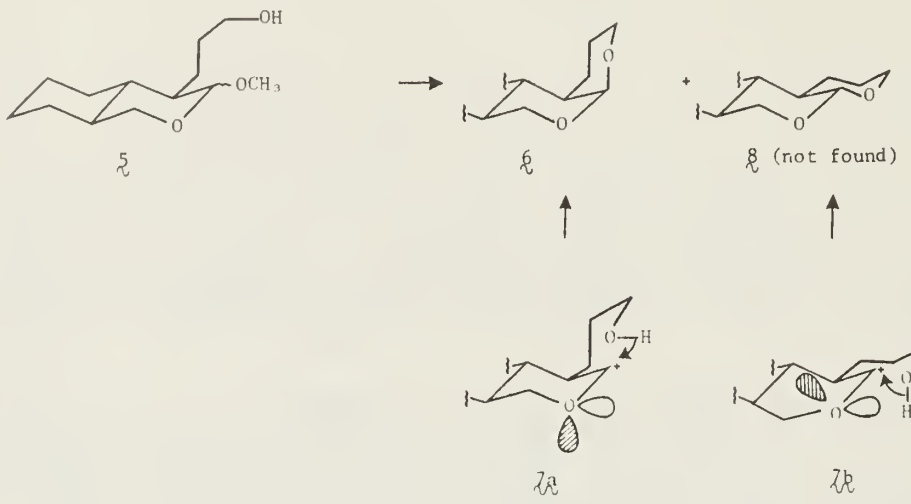
Kirby examined the hydrolysis of rigid acetals to give alcohol and hemiacetal products and calculated a $\Delta\Delta H^{\neq}$ between stereoelectronically assisted and non-assisted loss of alcohol to give the oxenium intermediate (Scheme I).[3,4] For acetals 1 and 2, 1 is 20 times more reactive than 2 because it can assume the conformer 1a with a lone pair app to the leaving alcohol (lone pairs participating in stereoelectronic control are shaded). This difference corresponds to a $\Delta\Delta H^{\neq}$ of 7 kcals. Kinetic studies of 3 and 4 yield $\Delta H^{\neq}$ of 2.8 kcal and 10.0 kcal, respectively. Again, a more facile cleavage with stereoelectronic control (3) is seen.

Scheme I



Stereoelectronic control is also important when forming acetals. Exclusive formation of acetal 6 from 5 under kinetic conditions can be explained by stereoelectronically controlled attack of the alcohol side chain on the carbenium ion intermediate 7 (Scheme II).[5] Stereoelectronically assisted β attack of the alcohol side chain (7a) to form 6 requires no conformational changes. To form 8 with stereoelectronically assisted attack requires the boat conformer 7b. This latter process is of higher energy and thus 8 is not seen.

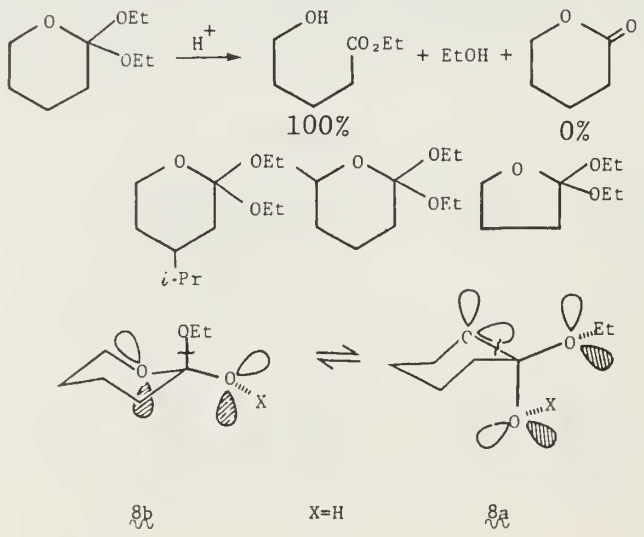
Scheme II



Reactions of orthoesters

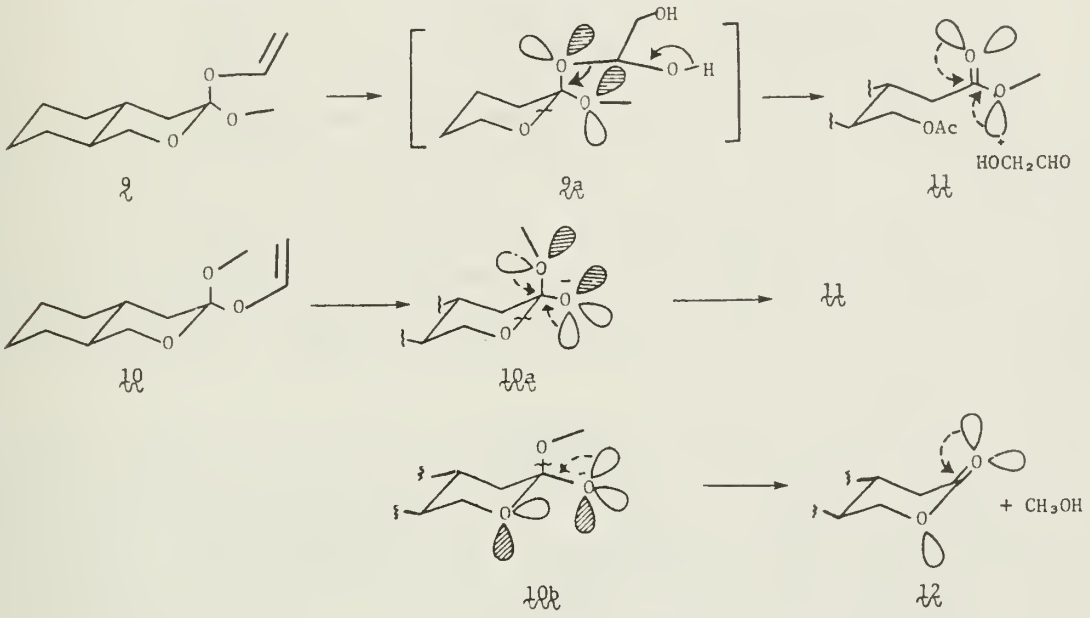
Hydrolysis of orthoesters is thought to occur through a three stage pathway that includes a carbenium ion and hemiorthoester intermediates.[6] Deslongchamps investigated the acid hydrolysis of a series of cyclic orthoesters (Scheme III).[7] He reported the hydroxy ester as the only kinetic product of these reactions. This result is explained by stereoelectronically assisted formation of the intermediate hemiorthoester 8a from the planar carbenium ion which introduces OH in the axial position. This conformation then must decompose to hydroxy ester before ring reversal to 8b allows for decomposition to lactone. Conformer 8b is not formed because the equatorial position has only one oxygen lone pair app to it (from the exo-oxygen). Capon reports that these results are not reproducible and that he finds 25-30% of the lactone is formed.[8] If this is the case, stereoelectronic breakdown of 8a is not more facile than ring inversion to 8b.

Scheme III



Oxidative cleavage of rigid vinyl orthoesters 9 and 10 and subsequent trapping of products with acetic anhydride/pyridine result in the exculsive formation of 11 (Scheme IV).[10] Stereoelectronic control predicts exclusive formation of 11 from 9 as can be seen from 9a. However, when 10 is examined it is seen that stereoelectronic cleavage can occur in two directions as shown with 10a and 10b. The exclusive formation of 11 from 10 is a result that cleavage as shown in 10a gives a more stable Z ester, 11, while cleavage of 10b gives an E ester (lactone), 12. Calculations have shown that Z esters are more stable because of σ conjugative interactions of lone pairs in the molecule (stereoelectronic effects) illustrated with dotted arrows in 11 and 12.[12] This effect as shown in 10a and 10b is called secondary stereoelectronic control and is responsible for cleavage as shown in 10a being more facile than that shown in 10b.

Scheme IV



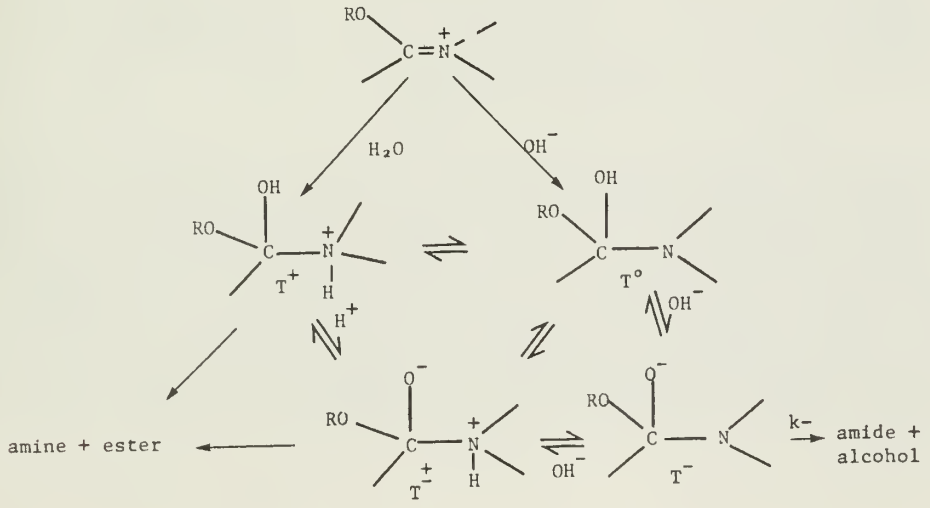
9 9a 11

10 10a 11

10b 12

Reactions with Hemiorthoamide Intermediates

Examination of the hydrolysis of imidates best serves to illustrate the currently accepted mechanism for the breakdown of hemiorthoamides.[11,12]

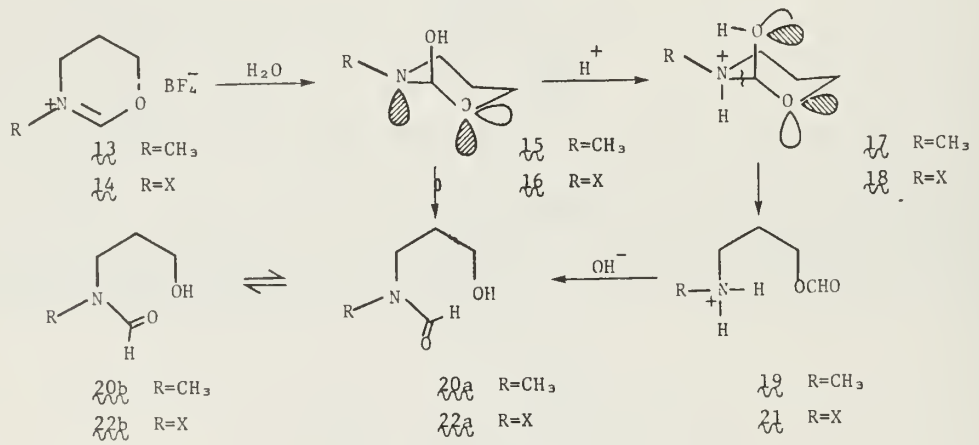


It is thought that the various forms of T determine the products of the reaction. T° is kinetically equivalent with $T^{\pm}$ and is discussed in terms of $T^{\pm}$. Ester amine products predominate at acidic and slightly basic conditions because of the predominance of T^{+} and $T^{\pm}$ which give this product. Amide alcohol products predominate at high pH because T^{-} is the predominant species.

Lehn and Wipff calculated the stereoelectronic properties of the protonated, T^{+}, and depronated, T^{-}, species of $CH(OH)_2NH_2$ and found that T^{+} exhibited selective weakening of the C-N bond and T^{-} exhibited unselective weakening of both the C-N and C-O bonds.[2] In both T^{+} and T^{-} these effects were found to be strongly dependent on conformation and are most pronounced when two lone pairs from the heteroatoms were app to the weakened bond.

Deslongchamps has examined the hydrolysis of imidate salts under both acidic and basic conditions.[13a-e] For trans salts imidate 13 and 14 under acidic conditions, he reports that 13 gives formatester amine 19 as the kinetic product (Scheme V). Treatment of 19 with base results in an initial 1:9 mixture of 20a and 20b, respectively, which equilibrates to a 4:6 ratio, respectively. Acid hydrolysis of 14 gives formatester amine 21 and formateamide alcohol 22a in a 1:1 ratio. Kinetic product 22a, as observed with ^{1}H NMR,[13b] equilibrates with the more stable 22b to give a 23:67 ratio, respectively. The unexpected formation of 22a from 14 arises because of steric hindrance to protonation of nitrogen. This allows the conformational change of 16 and subsequent formation of 22a to be competitive with formation of 18 and subsequently 21. When protonation of nitrogen is possible as with 13, the loss of this lone pair prohibits its participation in stereoelectronic control so 19 would be the only expected product.

Scheme V

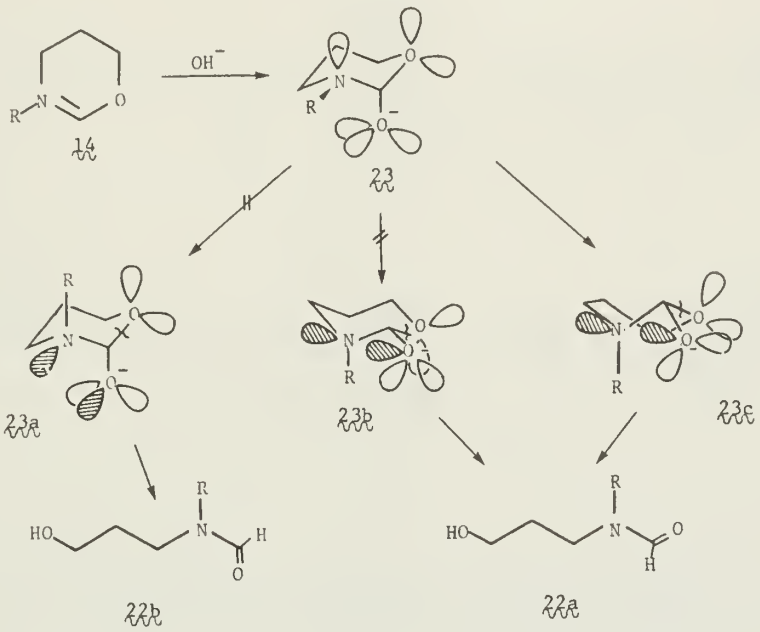


X=2,6-dimethylbenzene

Base hydrolysis of 14 (Scheme VI) gives 22a as the kinetic product and is therefore thought to proceed to product directly through the initial tetrahedral intermediate 23. Conformational change would be required for 23 to break down to observed products. As seen before, steric hindrance to the nitrogen of 14 would make conformational change competitive with stereoelectronic breakdown of 23. Investigation of the possible conformers 23a, 23b, and 23c finds the latter the best possibility. The conformer 23a can be ruled out because it would give 22b and 23b is less likely than twist boat 23c because it places the bulky R group

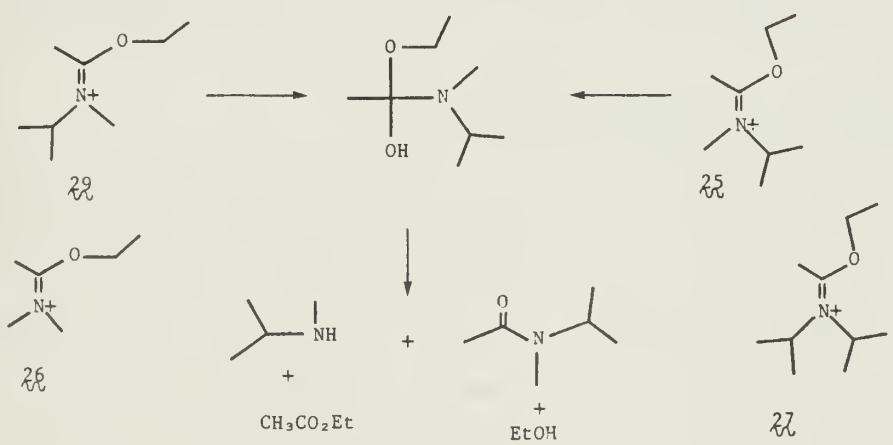
axial. Though the T° pH dependent mechanism seen earlier can also explain the products seen under both acid and base conditions, it can by no means explain the stereospecificity seen.

Scheme VI

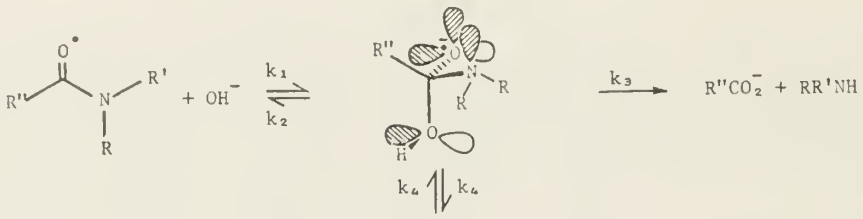


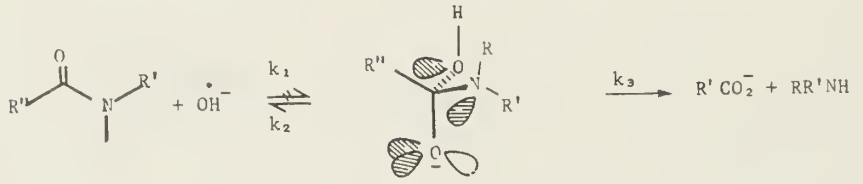
Schmir examined the hydrolysis of isomeric imidate ester salts 24 and 25 as a way of measuring the competition between stereoelectronic assisted bond cleavage and conformational change (Scheme VII).[14] Compounds 24 and 25 should behave as 26 and 27, respectively, if they decompose in a stereoelectronic fashion and thus transpose their geometry into products. Base hydrolysis of 26 and 27 give amide-alcohol yields of 80% and 6%, respectively, but 24 and 25 under basic hydrolysis both gave the same percent amide alcohol product. It is thus reasonable to assume that 24 and 25 go through the same intermediate. These results indicate that conformational changes in the hemiorthoamide tetrahedral intermediate can be competitive with stereoelectronic assisted bond cleavage.

Scheme VII



Deslongchamps has also observed competitive rates between stereoelectronic breakdown and conformational change in the base hydrolysis of amides. These rates become competitive for 3° amides when R", as shown below, is H, CH_3, or CH_3CH_2.[15]





28

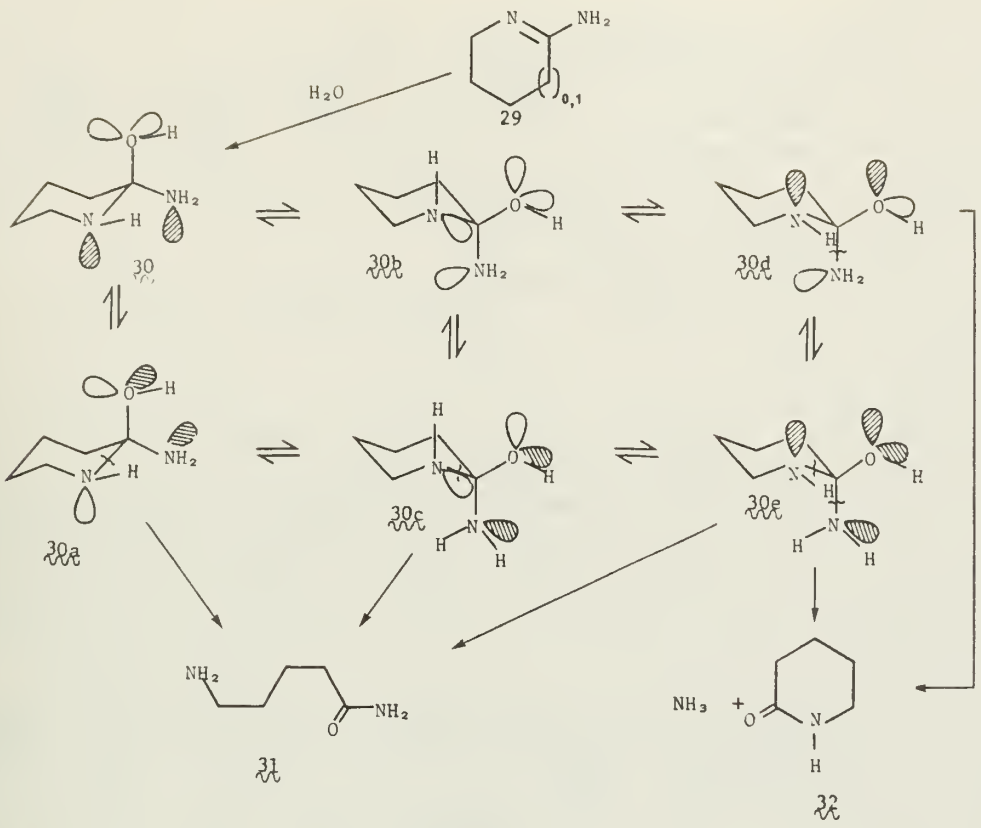
Using the scheme shown, Deslongchamps estimated the values for rate constants k_3 and k_4 and subsequently estimated $\Delta G^{\neq}$ values from this data for 3° amines. The following simplifying assumptions were made with this scheme: labelled oxygen lost from 28 is not likely to recombine with amine to form 28 again because of dilution in the solvent pool, interconversion of T^- and 28 proceeds at the same rate, k_4, hydrogen-heteroatom bonds are equivalent to lone pairs due to rapid proton exchange mechanisms, and $k_2 >> k_3$ because OH is a better leaving group than NRR'. From these assumptions, 1° and 2° amides should always show carbonyl oxygen exchange because the equivalence of hydrogen-nitrogen bonds and lone pairs cause T^- and 28 to be equivalent. Bender has shown that this indeed is the case.[16] For 3° amides this is not the case for they must rotate 60° and undergo N-inversion to form 28. Thus they should not undergo carbonyl oxygen exchange. However, it was found that they can undergo exchange when R" is small, H, CH_3 or CH_2CH_3 and R=CH_3 and R'=benzyl.[13e] With this system Deslongchamps estimated values for k_3 ranging from 1.1×10^8 to 1.0×10^9 s^{-1} and k_4 ranging from 5.7×10^6 to 3.2×10^8 s^{-1}, as R" increases in size. Estimated $\Delta G^{\neq}_3$ values ranged from 6.5 to 5.2 kcal/mol and $\Delta G^{\neq}_4$ values ranged from 5.2 to 5.8 kcal/mol, as R" increased in size. These results agree with stereoelectronically assisted cleavage being a more facile process than conformational change.

Further evidence for stereoelectronic control

A critical assumption made with stereoelectronic control is that the decomposition of the tetrahedral intermediate with stereoelectronic assistance occurs before ring reversal. This assumption is not always valid as has been seen in the above examples. Also, tetrahedral hemiorthoester intermediates similar to those postulated in Deslongchamps work have been observed by ^1H NMR[17] and U.V.[18] techniques so they must be long lived compared to conformational change.

Perrin reports that the results obtained from the hydrolysis of cyclic amidines 29 provide unambiguous evidence for stereoelectronic control (Scheme VII) Hydration of 29 would give the hemiorthamide intermediate 30 which cannot breakdown with stereoelectronic control, therefore, other conformers must be considered

Scheme VIII



Rotation about the external C-N bond gives 30a which can now decompose with stereoelectronic assistance to amino amide 31 or undergo ring reversal to 30c which also can give 31. Ring reversal of 30 would give 30b which again cannot undergo stereoelectronically assisted cleavage. Instead, it could undergo C-N bond rotation to give 30c or N-inversion to give 30d. Conformer 30d can now decompose to lactam 32 or with C-N bond rotation give 30e. Conformer 30e is also available from N-inversion of conformer 30c and can decompose to give both 31 and 32. The kinetic product of this hydrolysis is the aminoamide 31. Because ring reversal does not give conformers that lead to formation of the unobserved product it need not be considered. However, N-inversion does give conformers that can undergo breakdown to the unobserved product and it must be considered. Perrin compares the nitrogen inversion of this system with that of tertiary amines, 10^5 to 10^7 s^{-1},[20] and says that the assumption that stereoelectronic decomposition will occur before N-inversion is much better than that Deslongchamps must make with ring inversion. Also amides are not as strongly stabilized relative to lactams as esters are to lactones so this factor should not be as pronounced. Therefore, stereoelectronic control is the best explanation for exclusive formation of 31.

Summary

Stereoelectronic control in the decomposition of tetrahedral intermediates seems to be a plausible theory but its predictive capabilities appear to be limited to cases which show some conformational inflexibility.

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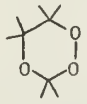
PHOTOGENERATION OF 1,2,4-TRIOXANES

Reported by Steve Wilson December 6, 1982

Introduction

1,2,4-Trioxanes are cyclic peroxides with the general structure shown in Figure I.

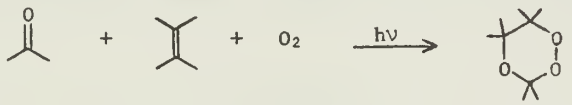
Figure I.



The formation of the 1,2,4-trioxane ring system has been proven by a variety of physical and chemical techniques, including X-ray crystallography.[1] In addition to the photochemical method that will be discussed in this report, 1,2,4-trioxanes have been prepared by the acid-catalyzed reaction of carbonyls with α-hydroxy hydroperoxides.[2] The decomposition of these cyclic peroxides in the presence of heat,[3,4,5] light,[5,6] and electron donors[5] has been studied. It has been proposed that trioxane decomposition is accompanied by chemiluminescence,[7] although this has never been conclusively proven experimentally.

Light-induced formation of 1,2,4-trioxanes, the first example being reported in 1971 by Werbin et. al.,[8] involves the condensation of a carbonyl containing compound, olefin, and molecular oxygen as shown in Scheme I.

Scheme I.



Besides providing a novel route to this unusual peroxide, this reaction has provided insight into the nature and reactivity of biradical or biradicaloid intermediates, especially those involved in the Paterno-Büchi reaction, the photochemical cycloaddition between excited carbonyls and olefins to yield oxetanes. In addition, the formation of 1,2,4-trioxanes has been shown to have biological importance, having been implicated as photooxygenation products of menaquinones (Vitamin K analogs), the photodeactivation of which has been shown to interrupt electron transport.

Scope of the Reaction

The reaction is initiated by irradiating the n,π* band of the carbonyl compound. A variety of light sources have been used, but it has been found that the highest yields of trioxanes are obtained using an argon ion laser.[1,5,9] There seem to be two reasons for this. First, since laser light is monochromatic it is possible to selectively irradiate the n,π* band of the carbonyl without exciting the resultant trioxanes, which are known to be extremely photolabile. Of course, it is possible to achieve this selective excitation by using filters. Since trioxanes are somewhat thermally unstable, however, and since their production is a low quantum yield process, conventional filtered light sources have proven to lack the necessary intensity to prevent partial thermal decomposition during photolysis. This points to the second

advantage of the laser, high intensity of the incident light.

Good yields of trioxanes have been obtained in a variety of solvents. Solvents that have been successfully employed include Freon-11 ($CFCl_3$), carbon tetrachloride, acetone, and methanol.[5] One solvent which did not work is acetic acid (vide infra).[1,5]

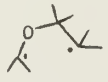
Temperature has been shown to be an important variable in trioxane formation. Yield enhancements of greater than 40% have been realized by conducting the reaction at -80°C rather than at room temperature.[5] It is believed that this yield enhancement may be due to the increase of oxygen solubility or to an increase in intermediate lifetimes at lower temperatures.

The oxygen pressure is another parameter that has a substantial effect upon trioxane yields. It has been found that by increasing the oxygen pressure from 1 atm to 11 atm an approximate twofold increase in trioxane yield (from 29% to 58% for a typical example) is realized.[5]

Unfortunately only a few carbonyl compounds have been shown to give trioxanes. To date, the only successful photogeneration of the cyclic peroxides utilizes a variety of quinones or benzophenone. The extremely low quantum yield for trioxane formation employing benzophenone may provide an explanation for this in terms of the stability of intermediate n,π* triplet carbonyl-olefin exciplexes[5] (vide infra).

In contrast to the low number of carbonyls that have been successfully employed, a large number of olefins have proven suitable for trioxane formation. Alkenes substituted with alkyl, allyl, aryl, acyl, and silyloxy groups have all given trioxanes in yields of 50% or greater.[5,10] For unsymmetrical olefins where there is the possibility of forming two regioisomeric 1,2,4-trioxanes, only the trioxane formally derived from oxygen trapping of the more stable preoxetane biradical (See Fig. II) is obtained. The only known

Figure II.



exception to this rule is vinyl acetate, which yields both regioisomers.

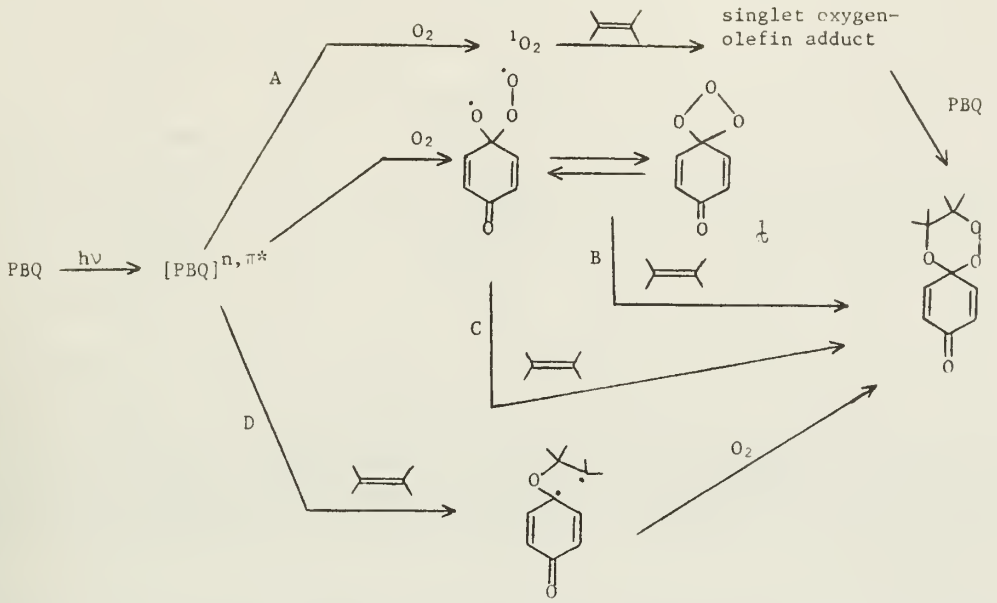
The Mechanism

Mechanistic studies concerning the photochemical formation of 1,2,4-trioxanes have been limited mainly to the reaction of p-benzoquinone (PBQ) with various olefins. As such, it may not be valid to extend conclusions concerning the mechanistic pathway of trioxane formation involving PBQ to all carbonyl compounds. In fact, the results obtained for PBQ may help explain why other carbonyls do not readily form trioxanes.

Four mechanistic pathways for trioxane formation have been considered.[1,5] They are outlined in Scheme II.

Pathway A involves the sensitized formation of singlet oxygen. Several lines of reasoning have been presented that make the involvement of singlet oxygen unlikely in trioxane formation. (1) Olefins have a larger rate constant, k_q, for excited PBQ quenching than does molecular oxygen ($k_{q\,styrene}$/

Scheme II.



$k_{qoxygen}$ = 5.9 for styrene).[5] (2) If a singlet oxygen-olefin adduct were involved in trioxane formation as in path A, it might be possible to trap the adduct with carbonyls other than PBQ. When the photolysis is conducted in acetone, however, only trioxanes incorporating the quinone are found, even though it is known that acetone-incorporating trioxanes are quite stable.[2] (3) Silyl enol ethers have been used to make trioxanes.[5] Silyl enol ethers are known to give characteristic rearrangement products upon reaction with singlet oxygen.[11] These rearrangement products are not found. (4) Electron deficient olefins, which are poor singlet oxygen substrates, give high yields of trioxanes.[10]

Pathway B which implicates trioxetane 1 as an intermediate has been ruled out as the result of an oxygen-18 labeling study. It was found that when oxygen-18 labeled molecular oxygen was used, the label was incorporated exclusively into the oxygens of the peroxide bond of the trioxane. The involvement of 1, in contrast, would predict scrambling of the label among the three oxygens of the trioxane ring.

Several lines of reasoning combine to make mechanism C unlikely also. It is known that oxygen quenching of low energy n,π* triplet carbonyls such as PBQ is very inefficient.[12] As mentioned earlier, a study of the relative quenching efficiencies of olefins and oxygen has shown olefins to be the better quenchers.[5] Although this does not positively rule out path C, path D seems much more likely, especially since there is positive evidence in support of it.

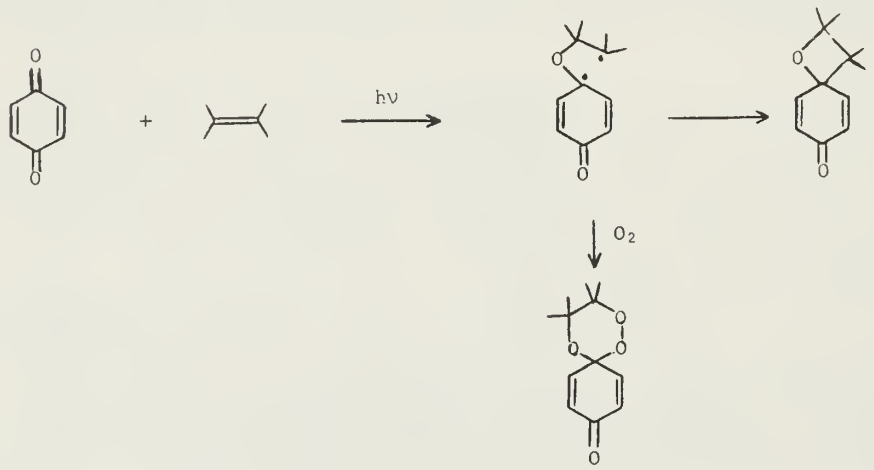
Evidence supporting pathway D has been obtained in the PBQ-t-butyl ethylene and PBQ-vinyl acetate systems. The reaction of PBQ with t-butyl ethylene under an oxygen atmosphere gives one of the possible isomeric trioxanes; vinyl acetate gives both.[5] If sulfur dioxide is substituted for oxygen, sulfones formally derived from trapping of the preoxetane biradicals (see Fig. II) are obtained. Again, t-butyl ethylene gives one isomer, vinyl acetate both.[5,13] This strongly suggests that oxygen and sulfur dioxide are both trapping an intermediate PBQ-olefin adduct.

Results from the PBQ-tetramethyl allene (TMA) system also support path D. In the anaerobic reaction of PBQ with TMA products derived from both of the possible isomeric oxetanes are obtained.[5] When the reaction is repeated in the presence of oxygen, the formation of the oxetane formally derived from the more stable allylic preoxetane biradical is completely quenched; the corresponding trioxane is formed instead. The yield of the other isomeric oxetane, which would be derived from a vinyl biradical, is unaffected or slightly enhanced by the presence of oxygen. It can be seen that path D provides the most straightforward interpretation of this result by assuming that two isomeric preoxetane biradicals are formed, one of which, the allylic one, has a long enough lifetime to be completely quenched by oxygen before closure to the oxetane can occur. The other, being a vinyl biradical, is less stable and closure to the oxetane, rather than oxygen trapping, predominates.

The spin multiplicity of the PBQ n,π* state involved in trioxane formation can be determined since it has been shown that a PBQ-olefin adduct as in path D of Scheme II is involved in trioxane formation. Bunce has shown by a series of quenching and sensitization experiments that PBQ reacts with olefins via the n,π* triplet.[14] Since trioxane formation also involves the initial interaction of PBQ and an olefin, it also should proceed from the n,π* triplet of PBQ.

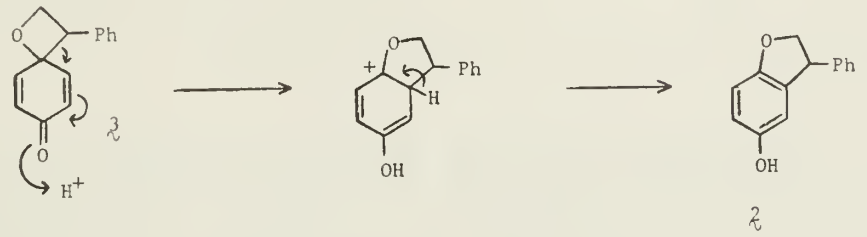
In summary, the experimental evidence suggests that the most straightforward mechanistic interpretation for trioxane formation involves oxygen trapping of a preoxetane biradical as shown in Scheme III.[5] Oxygen trapping of the biradical is found to compete with closure of the biradical to give an oxetane.

Scheme III.


O
O
+
hν
O
O
O

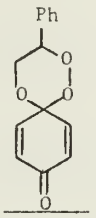
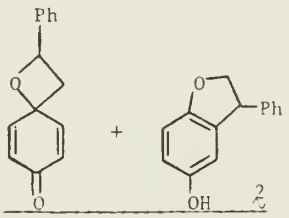
presence of styrene at various oxygen pressures in a relative quantum yield measuring device, the mixture of products shown in Table I is obtained.[5] The dihydrofuran 2 is assumed to arise from a facile dienone-phenol rearrangement of oxetane 3 as shown in Scheme IV.

Scheme IV.



It can be seen from Table I that there are two ways in which oxygen affects the reaction. There is the expected direct effect in which the trioxane yield increases with increasing oxygen pressure. Also, however, there is an indirect effect in which the oxetane yields are seen to increase at moderate oxygen pressures. The indirect effect can be explained as an en-

Table I.

Oxygen pressure(atm)	%PBQ consumed	%yield(based on consumed starting material) 	
10.8	82	94	--
1.0	28	41	15
0.2	18	19	10
0.0	12	0.0	8

hanced rate of spin inversion from the triplet preoxetane biradical in the presence of the paramagnetic oxygen to the singlet, which can close to yield oxetane.[16]

It will be noticed that at high oxygen pressures trioxane formation completely dominates (see Table I). This is inconsistent with the interaction of oxygen with only one intermediate since this would be expected to give a constant ratio of the trioxane to the two oxetane products at varying oxygen pressures.[5,17] Since the lifetime of the singlet preoxetane biradical is believed to be too short to allow for oxygen trapping, Wilson has proposed the formation of an intermediate that preceeds the triplet preoxetane biradical that can also be trapped with oxygen.[5]

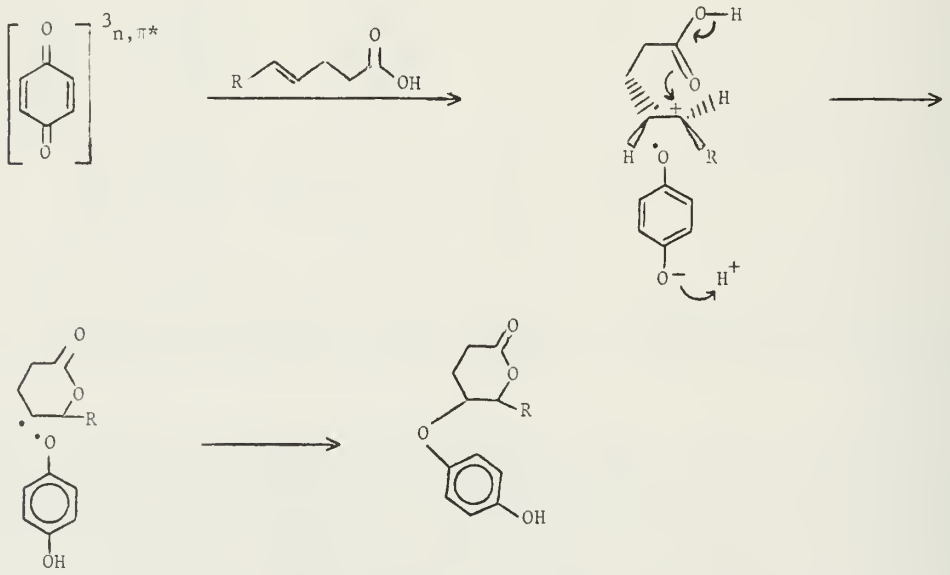
In a related experiment which provides further support for oxygen trapping of an intermediate that preceeds the triplet preoxetane biradical, t-butyl ethylene and PBQ were photolyzed under differing oxygen pressures.[5,18] It was found that both of the isomeric oxetanes were formed as well as a single trioxane formally derived from the more stable preoxetane biradical. It was also found that the ratio of the yields of the two oxetanes remained constant on going from an oxygen pressure of 0 atm to 11 atm, even though the

trioxane yield went from 0 to 43%. Thus, the trioxane is not being formed by selective oxygen trapping of the more stable preoxetane biradical, but rather, must be coming completely from a PBQ-t-butyl ethylene intermediate that occurs before partitioning into the two possible preoxetane biradicals.

The results of several studies have led to the conclusion that this PBQ-olefin intermediate that preceeds biradical formation is a charge transfer (CT)-exciplex. CNDO calculations[18] show the formation of such an exciplex both to be highly favorable and to have high charge transfer character, the olefin being the electron donor, PBQ the acceptor.

Several experimental findings support this conclusion. It has been observed in the PBQ-cyclooctatetraene (COT) system that when the reaction is performed in acetic acid the formation of trioxane is completely quenched, the only products being those expected from carbocation rearrangement initiated by acid trapping of a PBQ-COT adduct (see Scheme VI).[1] This acid trapping does not seem to be consistent with the nonpolar preoxetane biradical, but rather requires a polar intermediate. Similar results were obtained with norbornene in acetic acid.[5] In this example, however, trioxane formation was not completely quenched but was shown to occur in direct competition with the carbonium ion rearrangement products. The reaction of n,π* triplet PBQ with 4-pentenoic acids gives results that are readily explained by invoking a PBQ-olefin CT-exciplex[19] as shown in Scheme V. The spin and charge localization depicted in Scheme V is written as a conceptual aid and is not meant to imply such localization in the actual CT-exciplex. In a study of the anaerobic reaction of PBQ with

Scheme V.

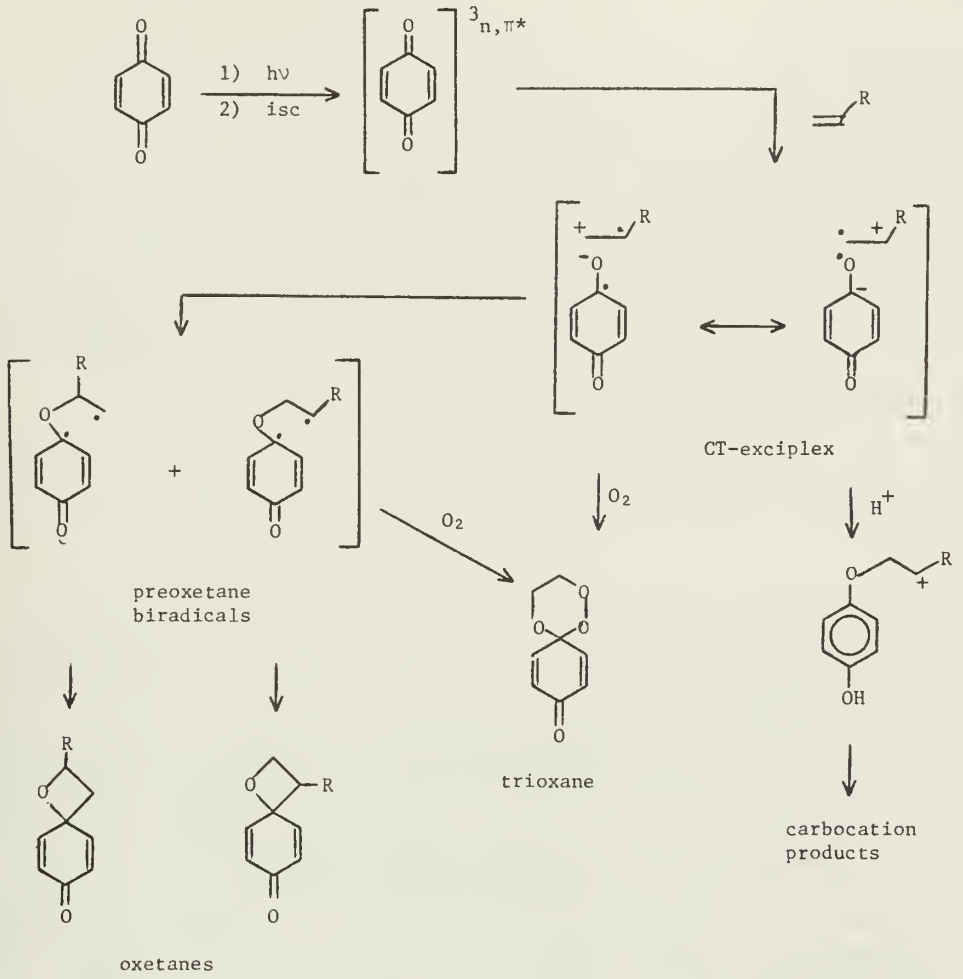


cyclooctene[14] it was observed that the formation of the product oxetane was slowed in polar solvent (acetonitrile), and that the possible radical cation trapping product, methoxy cyclooctene, was formed when the reaction was conducted in methanol. These results have been interpreted in terms of the formation of a CT-exciplex that can dissociate to radical ions in polar solvents.

There is an apparent contradiction in the above results, with some data seemingly favoring the oxygen trapping of biradicals and other experiments

supporting the trapping of CT-exciplexes. These facts have been reconciled by Wilson,[5] who has proposed the mechanism outlined in Scheme VI. It can be

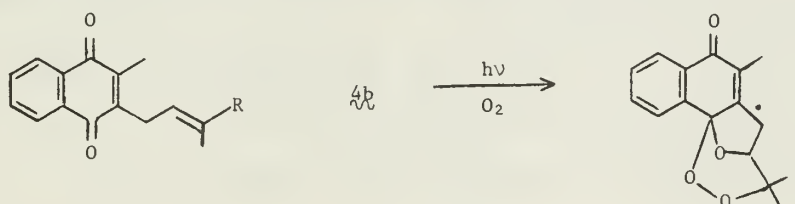
Scheme VI.



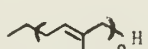
seen from the scheme that the proposed mechanism allows for oxygen trapping of both CT-exciplex and preoxetane biradicals along the reaction coordinate. It is postulated that which of the possibilities will occur is determined by the nature of these intermediates for the particular olefin involved.

Biological Significance

The photooxidation of Vitamin K, 4a, is known to deactivate electron transport in Mitochondria and other cell organelles.[20] Rapoport[21] has studied this photooxidation in vitro and found that the process does not involve singlet oxygen. Wilson[5,6] has examined the reaction of menaquinone 4b with oxygen and has found that it forms a stable 1,2,4-trioxane 5. Thus, it seems probable that the deactivation of electron transport may be due, at least in part, to the formation of a trioxane from Vitamin K.



4

a) R = 
b) R = CH_3

Summary

The scope of the photochemical formation of 1,2,4-trioxanes has been discussed. It has been shown that the major limitation of the reaction is to the type of carbonyl compounds that can be employed, possibly as the result of the stability (or lack of stability) of an intermediate CT-exciplex that is formed. The mechanism for the reaction has been examined; CT-exciplexes and preoxetane biradicals have been considered as pivotal intermediates that can be trapped by molecular oxygen. The possiblity of trioxane formation in biological systems has been presented. Many questions concerning this reaction remain unanswered. For example, how is the high degree of regioselectivity of the proposed oxygen trapping of CT-exciplexes realized? Is the oxygen trapping process concerted or stepwise? What are the important structure-reactivity characteristics of olefins that determine which, and to what extent the proposed carbonyl-olefin intermediates are trapped? These seem to be questions that presently cannot be answered.

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REACTIVE INTERMEDIATES IN CATALYZED DIAZOALKANE DECOMPOSITIONS

Reported by Charles Little December 9, 1982

The catalytic decomposition of diazoalkanes induced by metal containing salts and complexes is an example of a "carbenoid" reaction, so called because the products are formally carbene-derived even though no free carbene may be generated.[1] That the reactive intermediates are not the same as in the photolytic or thermal decomposition is usually only inferred from the different chemistry observed. For example, catalytic decomposition in the presence of suitable olefins usually gives cyclopropanes in higher yield than does photolytic or thermal decomposition but with suppression of typical carbenic processes such as C-H insertion or Wolff rearrangement (in the case of α-diazoketones).[2]

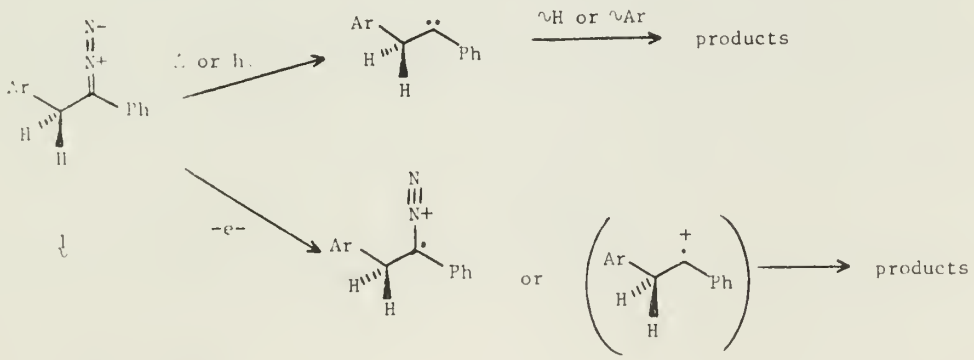
In many cases, a metal-diazo complex is invoked to explain this different chemistry. There can be little doubt that such complexes are sometimes formed, as several stable complexes have recently been isolated and characterized.[3] However, the role of these known complexes in typical carbenoid reactions, such as cyclopropanations, remains obscure.

A number of reports have appeared in the last decade, however, indicating that coordination to a metal center is not a distinquishing feature of carbenoid reactions.[4-8] In some instances organic electron acceptors have been found to mimic the catalytic activity of metal catalysts.[4-7] In other examples metal catalysts have been found to be involved only in initial electron transfer to produce diazo radical cations which then enter into chain reactions to yield typical carbenoid products.[8]

Whether diazo radical cations - or perhaps even carbene radical cations - may in general account for the different chemistry in carbenoid reactions remains to be seen. The chemistry of such intermediates is poorly understood as yet, largely because all of the mechanistic studies carried out to date have in common that the intermediates could only yield isolable products by intermolecular processes.

The impetus for the work reported here comes from the belief that a diazoalkane which can form products by a rapid intramolecular rearrangement in competition with intermolecular reactions will be a better model system with which to study the nature of the reactive intermediates involved in catalyzed decompositions.

Compounds of the general structure of 1 satisfy this criterion. The ability of 1 to form intermediates that can undergo rapid rearrangement has yielded some interesting insights that will be the subject of this seminar.



Ar = mesityl, phenyl

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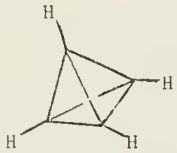
TETRAHEDRANE AND RELATED MOLECULES

Reported by Paul Cahill December 13, 1982

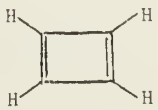
Tetra-tert-butyltetrahedrane 1, a sterically hindered derivative of the parent hydrocarbon 2, has recently been synthesized[1] after almost seventy



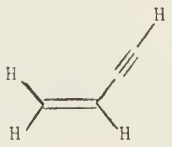
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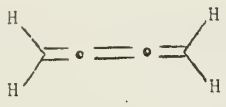


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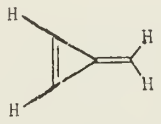


4

years of synthetic and theoretical study directed toward understanding this highly strained system. Tetrahedrane is the most strained member of the family of molecules with molecular formula C_4H_4. This group includes cyclobutadiene 3, vinyl acetylene 4, butatriene 5, and methylene cyclopropene 6.



5



6

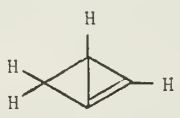
Unlike cyclobutadiene, for which the ground state geometry and multiplicity had been controversial for many years[2], all calculations of 2 show it to be an undistorted tetrahedron.[3] The electronic structure has been predicted by graph theory which shows filled doubly degenerate HOMOs.[4] This is unlike cyclobutadiene, which if square would have only half-filled HOMOs.

Extensive molecular orbital calculations have been published on many C_4H_4 molecules. Ab initio calculations using small basis sets such as STO-3G are numerous, but are of questionable value. Calculations using double zeta basis sets, such as 4-31G and 6-31G, yield more accurate data. Because of the expense involved in the better calculations, only very small areas of the potential surface of C_4H_4 can be studied by these methods. Recently, the semi-empirical method MINDO/3 was used to locate all of the local minima and some of the saddle points (which correspond to transition states) on the C_4H_4 hypersurface.[5]

The information available from a MINDO/3 calculation on a molecule includes a heat of formation for optimized geometric parameters. Although heats of formation calculated by MINDO/3 are often in error, the program has been used frequently to estimate the thermodynamic stability of new compounds. The ΔH_f^{298} calculated for molecules 2-6 is shown in Table 1. Two acetylene molecules are included as a reference. Two unknown molecules are also predicted by MINDO/3 to be stable, 7 and 8.



7



8

Table 1.

Compound		MINDO/3 ΔH_f	Expt'l.
Vinylacetylene	(4)	60.4 kcal/mol	72 kcal/mol
Butatriene	(5)	64.3	--
Methylenecyclopropene	(6)	81.0	--
Cyclobutadiene	(3)	94.4	--
Acetylene (x2)		115.5	108.6
Tetrahedrane	(2)	126.3	(unknown)
Bicyclobutene	(7)	120.0	(unknown)
Bicyclobutene	(8)	97.1	(unknown)

One method of determining the heat of formation of an unknown compound from an ab initio calculation is to use a known reference compound. For example, the total energies of cyclobutadiene and cyclobutene can be calculated. From the known heat of formation of cyclobutene, the difference in the calculated total energies, and estimated zero point energies, the heat of formation of cyclobutadiene can be calculated. The heats of formation of several C_4H_4 molecules have been calculated using this method. In Chart 1 the relative energies of the C_4H_4 hydrocarbons as calculated by MINDO/3 and ab initio plus CI are plotted.[6,7]



Chart 1. Relative heats of formation of C_4H_4 hydrocarbons by MINDO and by ab initio + CI calculation. For cyclobutadiene, MINDO/3 ΔH_f = 94.4 and ab initio plus CI ΔH_f = 105 kcal/mol.

The MINDO/3 and ab initio results are in poor agreement. The correct values are probably closer to the ab initio numbers. From this analysis it is apparent that isomerism from tetrahedrane to cyclobutadiene is exothermic on the order of 30 kcal/mol. This isomerism is orbital symmetry forbidden, and it is predicted to involve a biradicaloid intermediate.

Both MINDO/3 and ab initio plus CI calculations have been used to describe the minimum energy reaction path (MERP) between 2 and 3. The MERP is not a simple saddle point; it may involve up to two short-lived intermediates. The MINDO/3 MERP is diagrammed in Chart 2; the ab initio result is in Chart 3. Again the results are in poor agreement. The MINDO/3 barrier is only one-fourth the height of the ab initio barrier, although both methods predict the same geometry for the transition state. The structure 2a is predicted to be an intermediate by MINDO/3, but no local minimum corresponding to 2a was located by ab initio methods. The molecular structure 2c is a minimum in both calculations and is a singlet state. Structure 2b is the transistion state and it is calculated to be a triplet.

Many of the geometrical parameters of tetrahedrane are determined by the high (T_d) symmetry of the molecule. The carbon-carbon-hydrogen angle is 144° 44', and the dihedral angle between two adjacent faces is 70°32'.[8] Optimized C-C

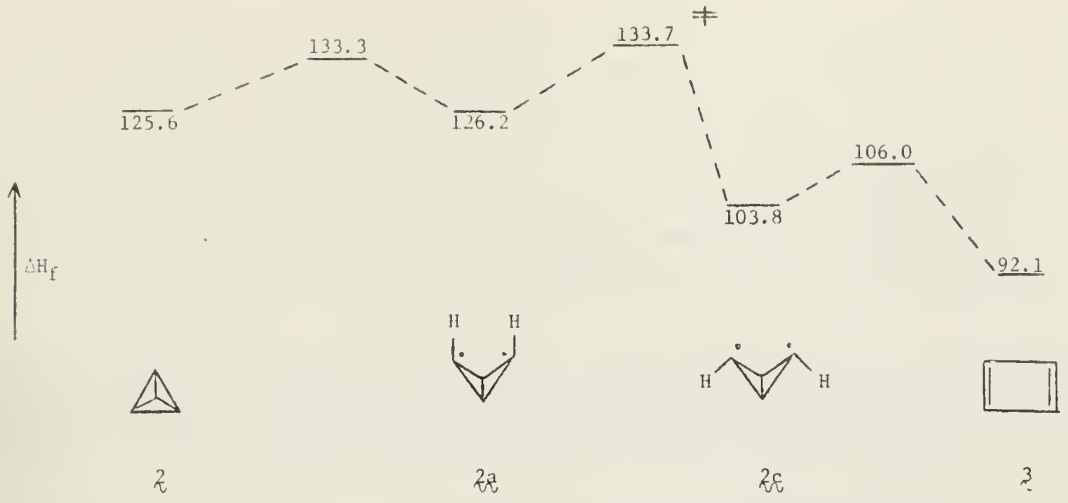


Chart 2. Tetrahedrane ⟶ Cyclobutadiene MERP at MINDO/3 level with CI. Two bicyclobutanediyl biradicals are predicted as short-lived intermediates.

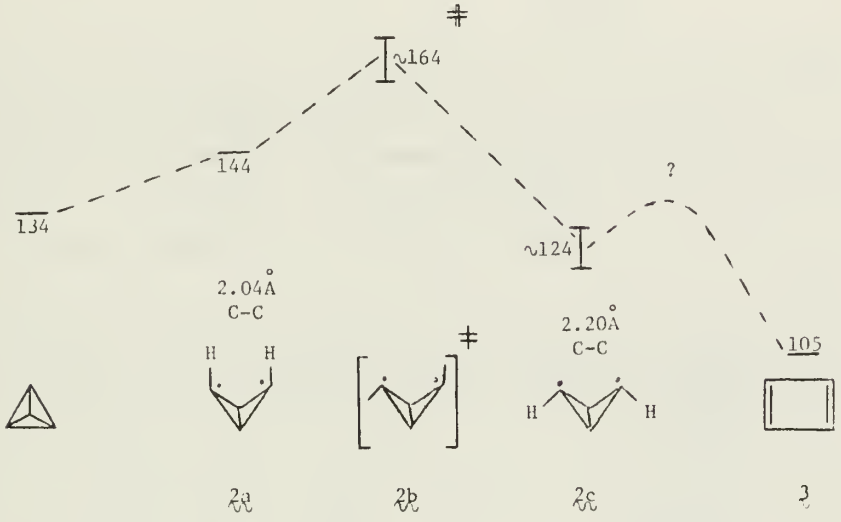


Chart 3. Tetrahedrane ⟶ Cyclobutadiene MERP at high level ab initio plus CI. The barrier between 2c and 3 was not calculated, but is expected to be small.

and C-H lengths are 1.501 Å and 1.082 Å by MINDO/3 and 1.470 Å and 1.064 Å by a CI ab initio calculation. For comparison, the observed dihedral angle between the faces in bicyclobutane is 126± 3° and the bridging C-C bond length is 1.54±0.02 Å.[9] Similarities also exist in the electronic structure of cyclopropane and 2. Tetrahedrane's C-C bonds are predicted to be "banana bonds" with approximately sp^5 hybrization. The valence electron density is predicted to have a minimum at the center of the molecule and at the center of each face. The maximum valence electron density is so far from the line connecting carbon atoms that edge protonation is estimated to occur at pH 16.[10]

Most calculations on tetrahedranes have focused on the parent hydrocarbon. However, there is experimental evidence that σ donating, π accepting ligands stabilize strained systems.[11] The effect of alkylating 2 was for many years

thought to be kinetically destabilizing because it was argued that the transition state biradical would be stabilized and thus the barrier to isomerization would be lowered. Of course, the steric effects which result from tert-butylation of the tetrahedrane were not properly considered. A MNDO calculation showed not only that the barrier to isomerization of 1 is expected to be within 5 kcal/mole of the barrier to isomerization of 2, but also that the ΔH_r of the isomerization drops from 45.9 to 6.7 kcal/mol.[12] The change in ΔH_r is attributed to crowding of the tert-butyl groups in the cyclobutadiene; and the X-ray structure of tetra-tert-butylcyclobutadiene shows distortion due to steric effects.[13]

Synthesis of the tetrahedrane framework requires the formation of four fused cyclopropanes and six carbon-carbon single bonds. A retrosynthetic analysis reveals several approaches to the tetrahedrane nucleus. Because this area has been extensively reviewed[14], only a brief summary of work prior to 1978 is presented.

Retrosynthetic cleavage of four bonds as shown in (1) leads to two ace-



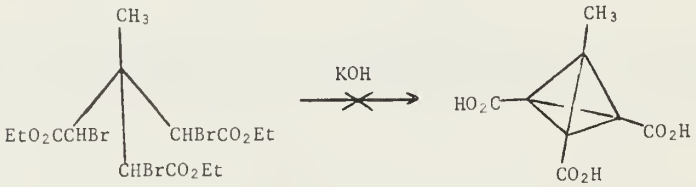
(1)

tylenes. In the synthetic direction this thermal reaction is orbital symmetry forbidden. Although this approach to the tetrahedrane framework was intensely studied, neither isolable tetrahedranes nor evidence for tetrahedrane intermediates were discovered. Both thermal and photochemical reactions were used.

Cleavage of three bonds retrosynthetically as in equation (2) demonstates



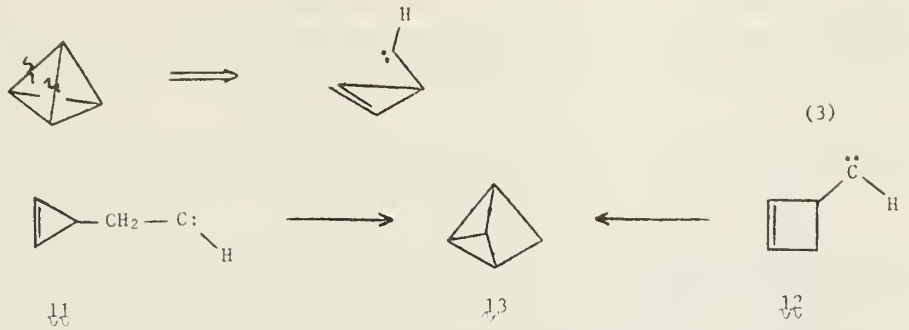
(2)



9 10

the first route attempted. In 1913 Beesly and Thorpe[15] treated 9 with aqueous alkali and claimed to have synthesized 10 in 13% yield. For many years this result was generally accepted, but in 1959 Larson and Woodward[16] were unable to reproduce the early work. This negative result spurred work in this area.

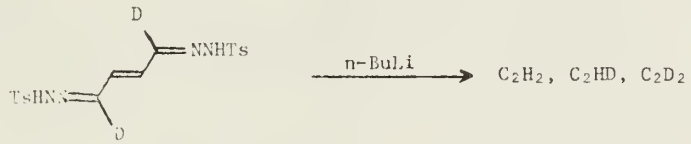
Addition of a carbene to a cyclopropene is shown retrosynthetically in equation (3). Despite the observation that both 11 and 12 gave the closely analogous isolable, tricycle 13[17], a tetrahedrane could never be isolated by this method. However, Rodewald and Lee in 1973 published their work on 14;



(3)

11 13 12

which when treated with n-butyllithium gave deuterium scrambled products.[18] A tetrahedrane intermediate was proposed.



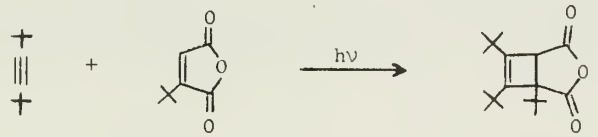
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The only retrosynthetic disconnection which led to the isolation of a tetrahedrane is shown in equation (4).



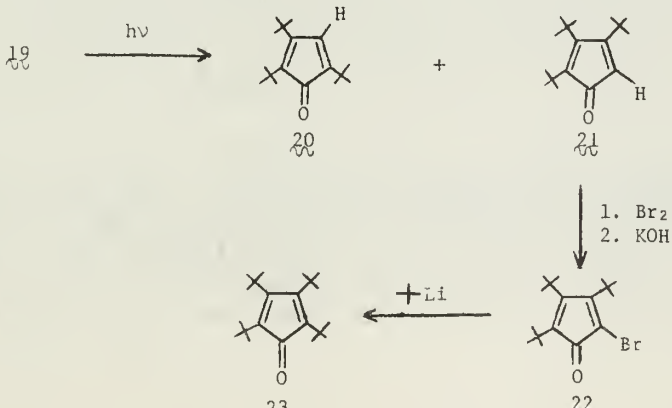
(4)

The synthesis of tetra-tert-butyletrahedrane 1 begins with the photoadditon of di-tert-butylacetylene to tert-butylmaleic anhydride to give 19 in 60% yield.[19] (The starting materials can be synthesized cheaply and in quan-



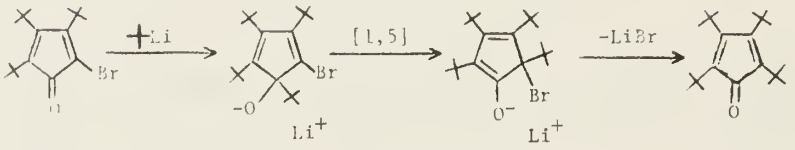
19

tity in several steps). Photolysis of 19 with an unfiltered low pressure mercury lamp gave 20 and 21 in 25% and 50% yield, respectively, after chromatography. Cyclopentadienone 21 was then treated with bromine followed by potas-



20 21 22 23

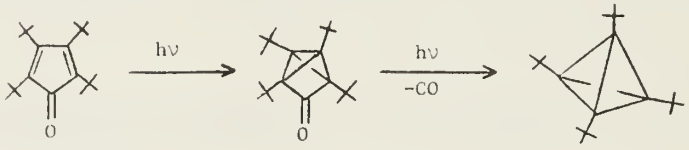
sium hydroxide to give 22 in 75% yield. Addition of the final tert-butyl group gives 23 in 22% yield.[20] The mechanism of this reaction is shown in equation (5).[21] Irradiation of 23 at 254nm results in the exclusive forma-



(5)

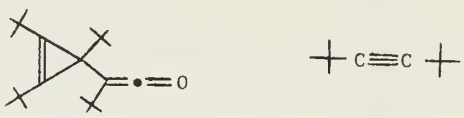
22 23

tion of 24. None of the expected housenone is formed. Extended irradiation



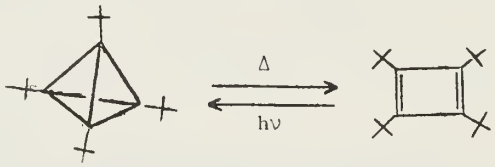
23 24 1

in ether at -100°C or in a hydrocarbon matrix at -196°K results in the loss of carbon monoxide and the formation of 1 in 40% yield based on 23 consumed.[23] Irradiation at higher temperatures results only in the formation of 25 and 26.



25 26

The assignment of the tetrahedral structure to 1 follows from a large number of physical measurements (an X-ray structure determination has not been completed). Compound 1 forms white air-stable crystals with a melting point of 135°, the temperature at which rapid isomerization of 1 to tetra-tert-butylcyclobutadiene 27 occurs. Irradiation at 254nm converts 27 back into 1.



1 27

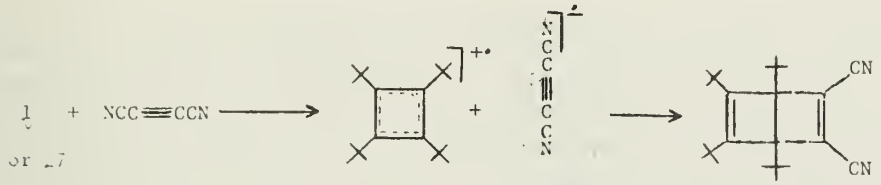
Compound 1 shows a singlet in the proton NMR spectrum at δ = 1.21 and three resonances in the ^{13}C NMR spectrum at δ = 9.27 (framework C), 27.16 ($\underline{C}(CH_3)_3$), and 31.78 (CH_3). Elemental analysis, osmometric molecular weight determination, and high resolution mass spectrometry all indicate the expected $C_{20}H_{36}$ composition.[23]

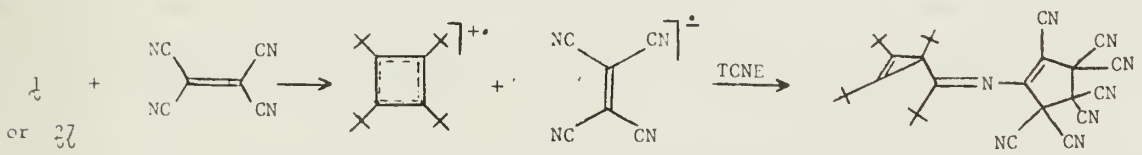
The IR and Raman spectra have been measured and the observed bands have been assigned assuming T_d symmetry. Averaged T_d symmetry on the ^1H NMR time scale has been confirmed by the lack of splitting of the ^1H resonance when 1 is dissolved in a liquid crystal. Low temperature (-50°C) solution ^1H NMR was used to investigate the barrier to rotation of the tert-butyl groups.

The ^1H resonance did not broaden. Confirmation of Mislow's prediction of a barrier to rotation of the tert-butyl groups will therefore require lower temperatures. The electron-impact mass spectrum fragmentation pattern shows only a small molecular ion peak, but the field ionization spectrum shows little fragmentation. The EI spectrum is nearly identical to the EI spectrum of di-tert-butylacetylene, providing additional evidence that vibrationally hot tetrahedranes dissociate to give acetylenes.

Tetra-tert-butyltetrahedrane is unreactive toward nucleophiles because the steric bulk of the tert-butyl protects the reactive nucleus. The tert-butyl groups cannot prevent oxidative electron transfer and oxidation to the radical cation is observed by a variety of reagents. The radical cation formed is unstable towards ring opening to form the tetra-tert-butylcyclobutadiene radical cation in which the unpaired electron is delocalized over the π system. Addition of $AlCl_3$ to a solution of 1 leads to the ring-opened radical cation, the low temperature ESR spectrum of which is identical to the tetra-tert-butylcyclobutadiene radical cation formed in the same way.[25] Treatment of 1 with $AlCl_3$ at room temperature leads to 27, as does electrolysis of 1.[26] No evidence for a dication, radical anion, or dianion has been uncovered.

Reaction of 1 or 27 with the electron acceptors dicyanoacetylene and tetracyanoethylene give the same products. The radical cation is believed to be the common intermediate:



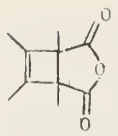
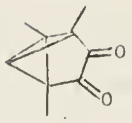
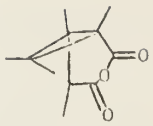
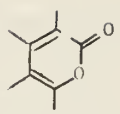
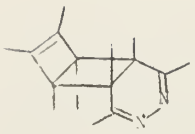
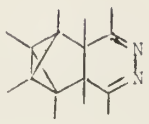
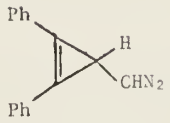
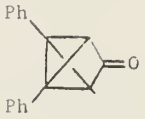
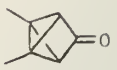


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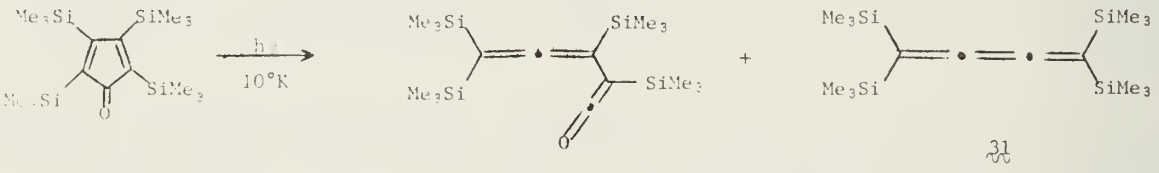
The structure of 28 was determined by an X-ray investigation. The low oxidation potentials for 1 and 27 are confirmed by a photoelectron spectrum. The vertical ionization energy of 1 is 7.50eV and of 27 is 6.35eV.

The cyclobutadiene isomer must be the thermodynamically favored product because 1 isomerizes to 27 upon heating. The ΔH of the reaction has not been measured, but the kinetics of the isomerization were found to be $\Delta H^{\ddagger} = 25.5 \pm 2.3$ kcal/mol and $\Delta S^{\ddagger} = -10.3 \pm 5.8$ eu.

Since the successful synthesis of 1, no other tetrahedrane has been observed or even positively identified as an intermediate in a reaction. The molecules below have all been used in attempts to synthesize tetramethyl-, dimethyl-, and diphenyltetrahedrane.[28-30] Furthermore, irradiation of 29

which might be expected to yield tetrakis(trimethylsilyl)tetrahedrane gave only 30 and 31 at 10°K.[31]



29 30 31

The possibility of an isolable tetralithiotetrahedrane was reported by Schleyer in 1978.[32] Irradiation of dilithioacetylene led to a crystalline compound which is stable at -20°C in the absence of air. Initial calculations on this C_4Li_4 system located two minima on the hypersurface, one corresponding to a rectangular cyclobutadiene structure with bridging lithium atoms; the other corresponding to a tetrahedrane with lithium atoms bridging each face. More recent calculations favor the cyclobutadiene structure. The report that the reaction of this C_4Li_4 molecule with methyl iodide led to tetramethyltetrahedrane[33] was retracted.[34] An X-ray structure analysis is planned.[35]

In light of all the work toward the synthesis of tetrahedranes, the high stability and ease of synthesis of 1 is remarkable.

The "corset effect", the hypothesis that the tert-butyl groups kinetically stabilize the tetrahedrane nucleus because lengthening of one of the tetrahedrane's carbon-carbon bonds can be shown to result in an unfavorable steric interaction between neighboring tert-butyl groups, is not consistent with ab initio calculations. The ab initio calculations suggest that the transistion state to isomerization occurs before significant steric interactions can occur. The corset effect has also been used to rationalize the formation of 1. Photoisomerization of 23 and 27 lead to criss-cross addition products. Molecules analogous to 23 and 27 which do not contain four tert-butyl groups do not give criss-cross addition products. In this case, the tert-butyl groups play a key steric role.

An alternative rationalization which is consistent with the ab initio calculations is that tetrahedranes are formed in many of these reactions, but that they are formed in highly excited vibrational states. These highly excited molecules then decompose, except in the case of 1. Compound 1 does not decompose because the tert-butyl groups provide an efficient absorber for this excess energy. Rapid vibrational relaxation by alkyl groups has been observed in molecular beams.[36]

In conclusion, much work remains to be done in this field. An experimental test for the "vibrational relaxation" rationalization might be possible if the tetra-n-butyl analog of 24 could be synthesized. Finally, the X-ray structure analysis of 1 will provide much needed structural information about the tetrahedrane nucleus.

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ORGANIC SEMINAR ABSTRACTS

Spring Semester, 1982-83

University of Illinois

School of Chemical Sciences

Department of Chemistry

University of Illinois

Urbana, Illinois

61801

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Spring Semester, 1983

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NICKEL(II) CATALYZED ORGANOMETALLIC-C_{sp^2} CROSS-COUPLING REACTIONS IN ORGANIC SYNTHESIS

Reported by David M. Simpson January 17, 1983

Coupling of organic substrates with formation of a carbon carbon σ bond is a crucial reaction in organic synthesis. One approach to this objective is Ni(II) catalyzed cross-coupling of organometallic reagents with other organic substrates. The catalytic cycle of the reaction probably consists of a sequence of steps involving a diorganometal complex as a key intermediate.[1]

A variety of substrates may be coupled with organometallics. Acetylenic, vinylic, and aromatic compounds containing, as leaving groups, halides,[2] sulfides[3] and thiols,[3b] a sulfonate,[4] selenides,[5] phosphates,[6] silyloxy,[7] and alkoxy[8] have been employed. Heterocyclic compounds also undergo coupling.[3b,c,9] Intramolecular cyclization of N-alkenylaniline derivatives can also be achieved.[10] Due to differing reactivities of the leaving groups sequential[11] or selective[5,12] couplings may be performed.

Most commonly, Grignard reagents are used as the organometallic species for the coupling reaction. Methyl, alkyl, allylic, and aryl Grignard reagents have been used;[2a,b] vinylic Grignard reagents exhibit isomerization and relatively low reactivity.[2a,13] Even t-butyl magnesium chloride has been coupled.[14] Organometallics of zinc,[9d] aluminum,[6a] and lithium[15] have also been used.

Nickel(II) salts, such as $NiCl_2$[7] and $NiBr_2$,[15] and Ni(II) complexed by ligands containing O, P, S, N, and C [16] have been used as catalysts. In general, complexation by bidentate tertiary phosphines is preferred for several reasons: 1) Higher catalytic activity than with monodentate phosphine ligands can be achieved.[2a] 2) The stabilizing effect of phosphine ligands on catalytically active species is most prolonged.[2a] 3) Competitive β-hydride elimination from alkyl Grignard reagents can be reduced.[17] 4) Isomerization of Grignard reagents can be reduced.[2a,14,17,18]

Generally, regio- and stereochemistry of vinyl substrates are conserved in the coupling reactions. However, 1,2-dihaloolefins isomerized to give non-stereospecific but stereoselective coupling products.[19] β-Bromovinyl ethyl ether also isomerized.[20] Use of $Ni(acac)_2$ resulted in loss of stereo- and regioisomeric purity in the reaction of silyl enol ethers.[7]

Grignard reagents which do or do not undergo racemization are resolved during coupling when chiral alkyl-[21] or alkylaminophosphines[22] are used as ligands for Ni(II). Chiral ferrocenylphosphines functionalized with a chiral aminoalkyl side chain, have also been used as ligands.[23]

The vast study of effects on the reactivity of Ni(II) catalysts with different ligands, the wide structural variety possible for organometallics, the need for methods for coupling sp^2 hybridized carbons to other organic moieties, and the possibilities for asymmetric syntheses make Ni(II) catalyzed cross-coupling reactions of potentially great usefulness in organic syntheses.

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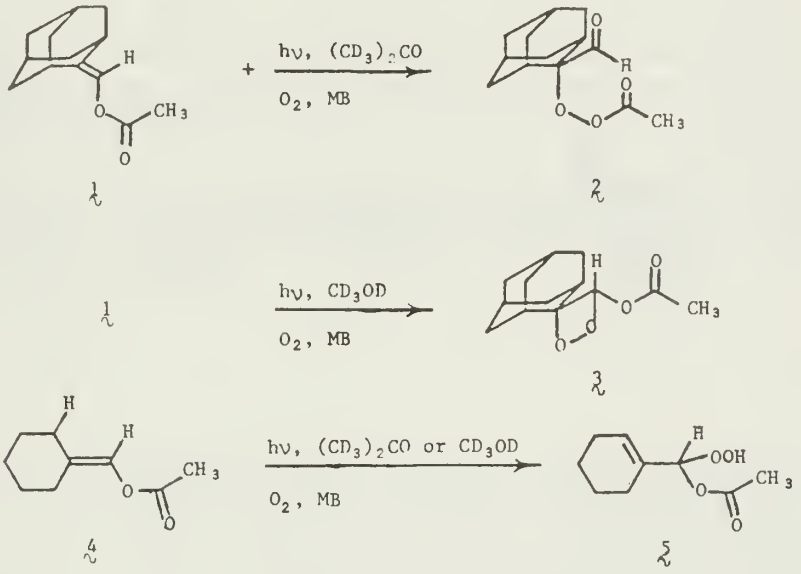
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REACTION OF SINGLET OXYGEN WITH ENOL ESTERS: A NEW PATHWAY AND MECHANISTIC IMPLICATIONS

Reported by Steve Wilson January 20, 1983

Singlet oxygen ($^1O_2$, $^1\Delta_g$), the lowest electronically-excited state of molecular oxygen, reacts with monoolefins in two basic ways: [2+2] cycloaddition to give a 1,2-dioxetane and the ene reaction yielding an allylic hydroperoxide.[1] Although the mechanisms for both of these reactions have been studied in great detail, much controversy still surrounds the subject. Some workers believe the reactions are concerted; others have postulated the involvement of various intermediates, including a 1,4-biradical, a 1,4 zwitterion, or a perepoxide.[2]

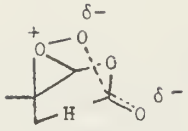
We have studied the reaction of singlet oxygen with olefins, specifically enol esters, in the hope of gaining further mechanistic insight into this reaction.[3] It was found that methylene blue (MB)-sensitized singlet oxygenation of the enol acetate of 2-adamantanecarboxaldehyde 1 results in a previously unknown reaction in which the acyl-shifted peroxyester 2 is formed. This product is formed in virtually quantitative yield in either acetone or carbon disulfide solution. However, if the reaction is performed in methanol, the major product becomes the dioxetane 3. Photooxygenation of enol acetate 4 gives neither acyl-shifted nor dioxetane product; rather, the sole product formed, 5, results from the singlet oxygen ene reaction.



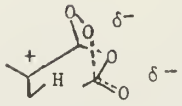
The rate constants for quenching of $^1O_2$ by these enol esters were determined by monitoring the decay of the phosphorescence characteristic of $^1O_2$ at different olefin concentrations.[4] The results are shown in Table I. It can be seen that the rate constants, which are nearly equal, do not reflect the dramatic change in product distribution discussed above. This observation tends to rule out a concerted path. We believe that the most straightforward explanation of these results involves the formation of a common intermediate whose fate depends on solvent and availability of allylic hydrogens. Furthermore, the observation of the novel acyl-migration product implies that this intermediate is dipolar in nature. We believe that the most likely possibility is the perepoxide 6 since the alternative open zwitterions 7 and 8 cannot give directly the acyl-shifted and ene products, respectively.

Table I.

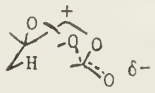
Enol Ester	Solvent	$k_q \times 10^{-4}$ s^{-1} M^{-1}
1	$(CD_3)_2CO$	3.4
1	CD_3OD	2.1
4	$(CD_3)_2CO$	7.5
4	CD_3OD	4.8



6



7



8

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RADICAL ANIONS IN A FLOWING AFTERGLOW

Reported by Joe Van Gompel January 24, 1983

Reactions in solution are often dominated by the properties of the solvent; acidity or basicity (Lewis or Brønsted), dipole moment, molecular polarizability, and various other effects of solvation. The study of reactions in the gas phase eliminates these effects.

Gas phase studies of cations are inherent in mass spectrometry. The study of anions in the gas phase has become popular more recently, with the development of instrumentation to generate and examine them in their diversity. Some of the methods of anion study in the gas phase include high pressure mass spectrometry,[1] ion cyclotron resonance spectrometry,[2] and flowing afterglow,[3] which is perhaps the most versatile technique of the three in terms of both scope of reactions and possible reaction conditions.

Figure I.

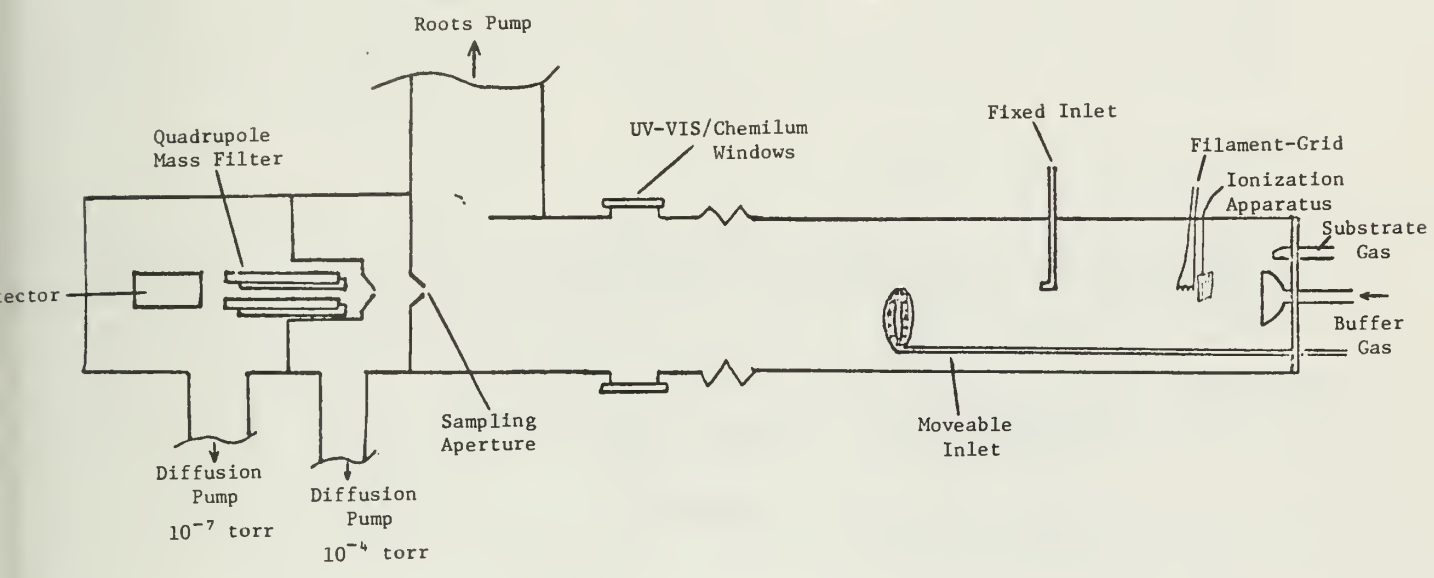


Figure I is an illustration of a typical flowing afterglow (FA) apparatus. The buffer gas, usually helium, is fed through a coarse frit-- pressures of 0.4 to 1.5 torr are typical. The substrate gas, usually from 10^{-4} to 10^{-7} torr, picks up an electron at the filament-grid and may undergo fragmentation to give a radical anion or an anion and a radical. The filament and grid have a potential difference of 30-150 V, which can be varied to give the desired degree of ionization. The reactant gas can then be added through either the fixed or moveable inlet. The flow rate is varied from $30ms^{-1}$ to $100ms^{-1}$ which, for a 1 meter flow tube, gives a residence time of 10 to 30 milliseconds. Thus, by varying the inlet position and measuring changes in a given product signal, rates of reaction can be determined.

The helium buffer is pulled off by a Roots pump, and a portion of the heavier product anions make it through the sampling apertures and differentially pumped chambers into the quadrupole mass filter, where the anion of proper m/e ratio is passed and measured by the detector. The temperature of the buffer gas has

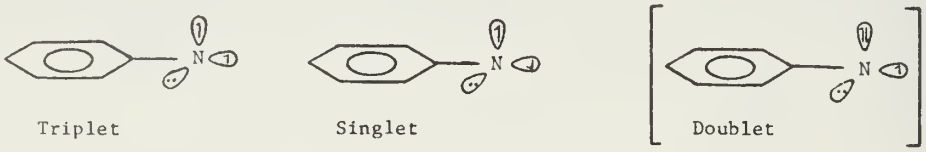
been varied from 80° to 600°K.[4] A microwave discharge has been used both to vibrationally excite N_2 substrate to 6000°K[5] and to ionize the substrate, in place of a filament-grid system.[6] As the name of the technique suggests, spectra can be recorded along with masses.[7]

A sample of studies done using the FA technique include reactions between negative ions and silylenol ethers to generate gas phase enolate anions,[8] rates and reaction modes of $C_3H_3^-$ ions generated by electron impact or by reaction of OH^- with allene or propyne,[9] reactions of alkyl nitrites with anions,[10] reactions of anions with N_2O and CO_2,[11] studies of S_N2 and E2 mechanisms,[12] and others.[13]

The study of radical anions in the gas phase proves far more versatile than studies in condensed phase in several ways. For example, radical anions can be generated in solution by either chemical[14] or electrochemical[15] reduction. Chemical reduction[14] involves the use of sodium naphthalide (Na^+ $Naph^{\cdot-}$) in THF solution to reduce diazo compounds to carbene radical anions. A vigorous reducing agent like $Naph^{\cdot-}$ seriously limits the types of reagents that can be used, effectively restricting such studies to product yields. Electrochemical reduction, on the other hand, requires a relatively polar solvent (DMF or CH_3CN in all cases cited) and potentials from $^-0.6$V to $^-2.4$V (vs SCE) for diazo diphenylmethane or diazofluorene, voltages high enough to react with some reagents, again limiting reactions. In the flowing afterglow, the solvent limitation simply does not apply, and only the desired reagent(s) need be exposed to the electron source and the other reagent(s) may be added in any sequence afterward.

PHENYLNITRENE RADICAL ANION

The phenylnitrene radical anion[16] was generated in an FA apparatus by dissociative electron attachment of phenyl azide, giving a signal at m/e 91, corresponding to $C_6H_5N^{\cdot-}$, with the M+1 peak height ruling out $C_7H_7^{\cdot-}$ as a possibility. Being a radical anion, this species can be neither a singlet nor a triplet, but is a doublet.



As an anion, it is unusual in that it does not have a closed-shell configuration. The unpaired electron was proposed on theoretical grounds to be in the in-plane orbital on nitrogen.[17] Thus, the charge density would be delocalized throughout the π-system. The π-system would still, however, have the largest coefficient on the nitrogen, making this the "basic" site on the ion.[16d]

When generated in the presence of excess phenyl azide, typical radical reactions such as dimerization and coupling with unreacted material occur to give peaks at m/e 182 and 210.[16a]

$$\underset{\text{m/e 91}}{PhN^{\cdot-}} + PhN_3 \longrightarrow \underset{\text{m/e 182}}{PhN=NPh^{\cdot-}}$$

$$\downarrow \longrightarrow \underset{\text{m/e 210}}{Ph-N=N-N=N-Ph^{\cdot-}}$$

The rate constant for the reaction of $\underset{\sim}{1}$ with phenyl azide was reported at k$\sim$ 10^{-12}cm^{3}molecule^{-1}sec^{-1}, which is roughly 5x10^{8}l mol^{-1}sec^{-1}.

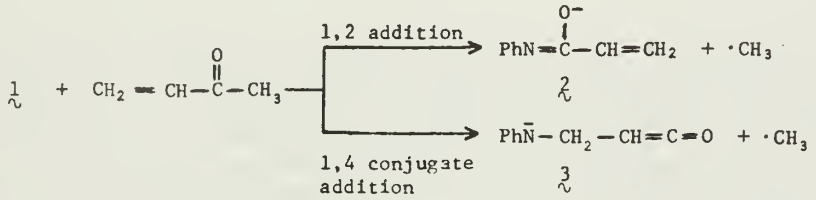
In reactions with various α,β-unsaturated carbonyl compounds,[16b,e] $\underset{\sim}{1}$ showed a marked affinity for 1,2-carbonyl addition, with proton abstraction occurring as a major reaction pathway only with more acidic molecules, such as 1,1,1-trifluoroacetone (see Table I). The proton affinity PA of $\underset{\sim}{1}$ has been deter-

Table I. Reaction of 1 with selected carbonyl compounds

Compound	Products [Assumed Neutral]	Fraction of Production Signal	ktotal cm^{3}molecule^{-1} sec^{-1}	Reference
CH_3CHO	$PhNCOCH_3^-$[+·H]	0.59	8x10^{-11}	16b
	$PhNCHO^-$[+·CH_3]	0.31		
	H_2CCHO^-[+·PhNH]	0.10		
CH_3COCH_3	$PhNCOCH_3^-$[+·CH_3]	0.81	6.5x10^{-12}	16b
	$CH_2COCH_3^-$[+·PhNH]	0.19		
CF_3COCH_3	$PhNCOCF_3^-$[+·CH_3]	0.36	9x10^{-10}	16b
	$PhNCOCH_3^-$[+·CF_3]	0.15		
	$CF_3COCH_2^-$[+·PhNH]	0.49		
$CH_3CO_2CH_3$	$PhNCOCH_3^-$[+·OCH_3]	0.88	1.5x10^{-13}	16b
	$CH_2CO_2CH_3^-$[+·PhNH]	0.12		
$CH_3COCOCH_3$	$PhNCOCH_3^-$[+CO+·CH_3]	0.98	6.5x10^{-10}	16b
	$CH_2COCOCH_3^-$[+·PhNH]	0.02		
$CH_2=CHCOCH_3$	$C_2H_4CONPh^-$[+·CH_3]	0.82	6x10^{-11}	16e
	$PhNC_2H_2COCH_3^-$[+·H]	0.02		
	$PhNCOCH_3^-$[+·C_2H_3]	0.05		
	$CH_2COCHCH_2^-$[+·PhNH]	0.11		
$CH_2=CHCHO$	$CH_2CHCONPh^-$[+·H]	0.97	2x10^{-10}	16e
	$PhNCHO^-$[+·C_2H_3]	0.03		

mined to be on the order of 372 kcal mol^{-1} through comparisons with known compounds[18] by both FA and ICR methods.[16c,d]

The major reaction with methyl vinyl ketone in Table I is written indicating 1,2 addition ($\underset{\sim}{2}$) instead of 1,4 conjugate addition ($\underset{\sim}{3}$), both of which would give the same m/e 146 signal following loss of ·CH_3. Since absolute structure



cannot be determined easily in this case because the m/e 146 signal could be due to either $\underset{\sim}{2}$ or $\underset{\sim}{3}$, some method of distinguishing the two by mass alone had to be used.

It had been observed[16d] that when various alcohols were reacted with $\underset{\sim}{1}$, two types of signals were seen. One type corresponded to the $PhN^{\cdot-}$ (ROH) cluster, and the other type corresponding to RO^-(ROH)x, where x has been observed as high as 4 for H_2O. The degree to which the RO^-(ROH)x signals are observed compared to $PhN^{\cdot-}$(ROH) depends on the degree of deprotonation of ROH. Comparison of the amounts of these two types of signals gives us PA data. Using these principles and the idea that $\underset{\sim}{2}$ and $\underset{\sim}{3}$ should have different PAs led to the determination of the ratio of $\underset{\sim}{2}/\underset{\sim}{3}$.

The PAs of 2 and 3 were estimated by comparisons with known compounds of similar structure. The acetanilide anion ($PA(PhNCOCH_3^-)$= 353 kcal mol^{-1}) was used as the model for 2. Replacing the methyl group of the acetanilide anion with a vinyl group as in 2 should offer some stabilization, giving PA 2<353 kcal mol^{-1}. Similarly, 3 was compared to the anilide anion ($PA(PhNH^-)$= 368 kcal mol^{-1}. The substitution of H with the methylene ketenyl group may offer some stabilization, but probably no more than 5-8 kcal mol^{-1}, giving PA(3)≥360 kcal mol^{-1}. Thus, there should be >7 kcal mol^{-1} difference in proton affinities between 2 and 3, which should be sufficient to differentiate between the two when compared to compounds of known PA. When run with H_2S ($PA(HS^-)$= 354 kcal mol^{-1}), CH_3CO_2H ($PA(CH_3CO_2^-)$=348 kcal mol^{-1}), and HCO_2H ($PA(HCO_2^-)$=345 kcal mol^{-1}), only the m/e 146 + HA signals were observed, meaning that PA(2 or 3)≤345 kcal mol^{-1}, suggesting that the structure of the m/e 146 ion is exclusively 2.

Changes in the pressure and flow rate from 0.4 torr and 80 m sec^{-1} to 1.1 torr and 36 m sec^{-1} gave no change in overall rate k or product distribution. It should be pointed out, however, that k is significantly lower (by a factor of 30) than predicted collisional calculations would suggest, indicating that 1 does not react with MVK on every encounter. The reasons for these observations may be that the energy required to push an encounter group over the activation energy barrier is not possessed by every reactant molecule or ion, or the orientations of the two species may be very important for reaction.

CYCLOPENTADIENYLIDENE RADICAL ANION

The cyclopentadienylidene radical anion 4 was generated via dissociative electron attachment on diazocyclopentadiene.[19] Like 1, 4 is a doublet species with a $\sigma^1\pi^2$ configuration. This has been suggested by M.O. calculations[20] and



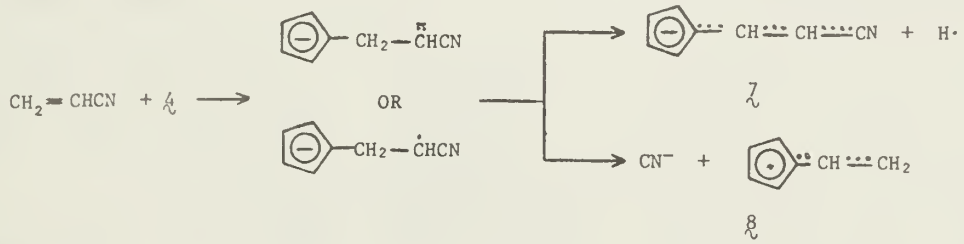
4 5 6

shown by analysis of the ESR in an argon matrix at 4K.[21] Comparisons with compounds of known PA[18] establish a PA(4)= 377 kcal mol^{-1}. As with 1, 4 tends to couple with excess starting material to give 5 and 6, 64% and 22%, respectively, along with 14% of the hydrogen atom abstraction product $C_5H_5^-$. Studies done with methyl halides suggests that the dissociation energy for $C_5H_5^- \rightleftharpoons C_5H_4^- + H\cdot$ is between the XH_2C-H dissociation energy of CH_3Cl($D°$= 101 kcal mol^{-1}) and CH_3Br ($D°$= 102 kcal mol^{-1}).[19b,22]

Table II. Reaction of 4 with selected compounds.[19]

Compound	Products [Assumed Neutral]	Fraction of Production Signal	ktotal $cm^3molecule^{-1}sec^{-1}$
CH_3F	No Reaction Observed	--	$\leq 10^{-13}$
CH_3Cl	$C_5H_5^-$ [+· CH_2Cl]	0.99	9×10^{-12}
	Cl^- [+· $C_5H_4CH_3$]	0.01	
CH_3Br	Br^-[+· $C_5H_4CH_3$]	0.81	1.3×10^{-10}
	$C_5H_5^-$[+· CH_2Br]	0.19	
$CH_2=CHCN$	$C_5H_4CH=CHCN^-$[+· H]	0.31	8.2×10^{-10}
	CN^-	0.57	
	m/e52 ($C_3H_2N^-$)	0.10	
	$C_5H_5^-$[+· C_3H_2N]	0.02	
$CH_2=CHCO_2CH_3$	$C_5H_4CH=CHCO_2CH_3^-$[+· H]	0.74	1.1×10^{-10}
	$C_5H_5^-$[+· $C_4H_5O_2$]	0.26	
$CH_2=CHCl$	Cl^-	0.88	2.3×10^{-11}
	$C_5H_5^-$[+· C_2H_2Cl]	0.12	
$CH_2=CHF$	No Reaction Observed	--	$\leq 10^{-13}$

The reaction of 4 with acrylonitrile bears comment (see Table II). Three of the four products, due to H·abstraction, protonation to yield $C_5H_5^-$, and conjugate addition followed by H·ejection are reasonably straightforward mechanistically. The route leading to CN^- (which is the primary product) is not immediately obvious. Increasing the pressure of the He buffer gas from 0.4 torr to 0.9 torr leads to a decrease in the CN^- signal and an increase in the addition product 7, which suggests that 8 is due to the decomposition of an intermediate species as opposed to being from a primary reaction path. Formation of 8 would



involve hydrogen migration to give a π-delocalized vinyl cyclopentadienyl radical.

Analogous reaction with the cyclopentadiene anion $C_5H_5^-$ 9[23] gives only one



9

product signal at m/e 118, corresponding to conjugate addition of the delocalized anion. Evidently the radical intermediate yielding 7 and 8 is significantly less stable than its anionic counterpart 9 with respect to decomposition products. 9 was also found to have a PA 21 kcal mol^{-1} less than 4 (PA 9 = 356 kcal mol^{-1})[18] and to be considerably less nucleophilic than 4.[24]

SUMMARY

The flowing afterglow has been presented as a very versatile and powerful technique in studying reactions in the gas phase. This paper has discussed the radical anions 1 and 4 as generated in a FA; their PAs were determined by comparison of materials of known PA, and reactions with various other compounds, reaction rates, and product studies were done. Continued research with FA should elucidate many more gas phase reactions in the future.

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21. 19b, Ref. 11
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24. Let $k_\Delta = k_4/k_2 \cdot K_{\Delta\ CH_3Br} = 40$, $k_{\Delta,\ CH_2=CHCN} = 39$, $k_{\Delta,\ CH_2=CHCO_2CH_3} = 59$. k_2, CH_3Cl was too slow to measure; $k_{2CH_3Cl} \leq 10^{-13}$ $cm^3 molecule^{-1} sec^{-1}$.

THE $S_{ON}2$ MECHANISM

Reported by Scott H. Bergeson January 27, 1983

The $S_{ON}2$ mechanism is a bimolecular mechanism for nucleophilic substitution in which the bond-forming and bond-breaking steps occur in the one-electron oxidized substrate (its radical cation). Roger W. Alder named it $S_{ON}2$ for oxidatively initiated nucleophilic substitution and proposed the reaction sequence shown in Scheme I.[1]

Scheme I.

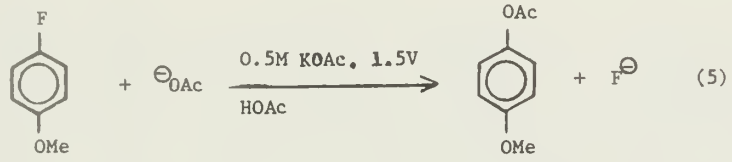
$$ArX \xrightarrow{-e^{\ominus}} (ArX)^{+\cdot} \quad (1)$$

$$(ArX)^{+\cdot} + Nu^{-} \longrightarrow \dot{A}r(Nu)X \quad (2)$$

$$\dot{A}r(Nu)X \longrightarrow (ArNu)^{+\cdot} + X^{-} \quad (3)$$

$$(ArNu)^{+\cdot} + ArX \longrightarrow ArNu + (ArX)^{+\cdot} \quad (4)$$

In contrast to the $S_{RN}1$ mechanism which Nancy Peacock reviewed,[2] and which occurs under reducing conditions, the $S_{ON}2$ mechanism requires oxidizing conditions. For example, Nyberg and Wistrand found that 4-fluoroanisole undergoes substitution by acetate ion (equation 5) under anodic oxidation, although this is not formally an oxidation process.[3]



(5)

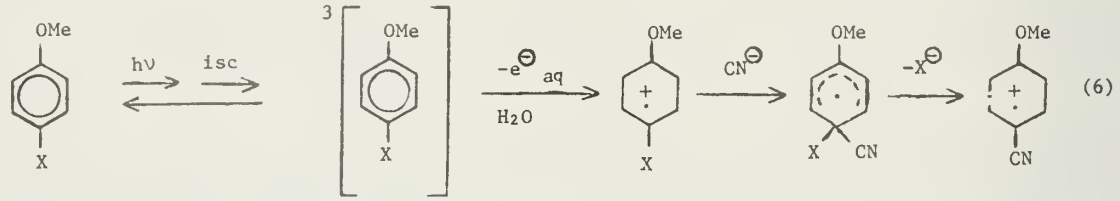
Thus oxidative initiation provides a means of activating aryl halides towards nucleophilic substitution. In practice, however, there is some limitation on the combination of substrate and nucleophile. The substrate must be more easily oxidized than the halide $X^{\ominus}$ and the nucleophile $Nu^{\ominus}$ if the current yield $[mol(product)F^{-1}]$ is to be greater than 1. In addition the product should be more resistant to oxidation than the substrate if high conversion is to be practical. In the above example the current yield decreases from 270% at 2% conversion ($F\ mol^{-1}$) to 84% at 200% (calculated as 1 $F\ mol^{-1}$) conversion[4] while polymeric material from further oxidation of 4-acetoxyanisole becomes clearly visible.

Photochemical initiation provides a convenient route into this mechanism. Irradiation of 4-fluoro- and 4-chloroanisole at 280 nmin a solution of cyanide in tert-butyl alcohol/water with 2 M acetone as sensitizer provides clean and efficient cyanodehalogenation in yields greater than 90%.[5] In dilute solutions (less than 10^{-3} M in ArX) in t-BuOH/H_2O (1:3) the quantum yields reach upper limits of respectively 0.50 and 0.55 at $[CN^{-}] = 5x10^{-2}$ M while photohydrolysis occurs at lower concentrations of cyanide. The quantum yield is strongly dependent upon the ratio of tert-butyl alcohol to water. The quantum yield of photocyanation of 4-fluoroanisole at $[CN^{-}] = 0.17$ M increases from 0.01 to 0.69 on increasing the mole fraction of water from 64% to 99%. The authors attribute this effect to the solvent polarity. The lack of quenching of fluorescence by cyanide indicates that the reaction most likely proceeds through the triplet state. The photosubstitution of haloanilines has also been reported to be a triplet reaction.[6] In studies of various fluoroanisoles, di- and trimethoxy-

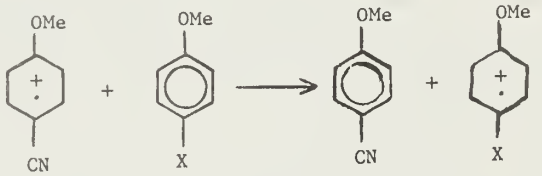
benzenes, den Heijer et al. found that methoxy groups appear to exert both an activating and an ortho/para directing effect in nucleophilic photosubstitution.[5] The loss of an electron from the triplet, yielding the radical cation of the aromatic compound, as the initial chemical step would obviate this apparent anomaly.

Grossweiner and Joschek[7] found that photochemical formation of solvated electrons in aqueous solution is favored for aromatic compounds with low gas phase ionization potentials, negative Hammett σp constants and low reactivity towards $e^{\ominus}_{aq}$. Since den Heijer observed that the quantum yield of photosubstitution is independent of the intensity of the exciting radiation, ionization of the triplet must be a one-photon process in aqueous media. In aqueous solution the respective quantum yields of photocyanation of 4-fluoro- and 4-chloroanisole are 0.70 and 0.80, compared to the quantum yield of intersystem crossing for anisole which is 0.74.[8] Thus, nearly all triplet molecules formed lead to substitution products.

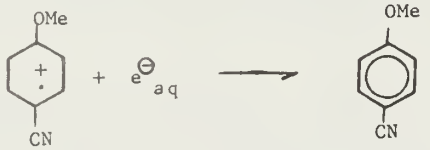
Ionization of the triplet may well be less efficient when the solvent is less capable of solvating the radical cation and the electron. "The curious phenomenon that at higher concentrations of para chloroanisole (10^{-3}M) the quantum yield becomes higher than 1 (1.2)"[5] provides further evidence that the reaction occurs via ionization of the substrate and that an electron can be transferred from a substrate molecule to a product radical cation in this type of reaction (equations 6-8).



(6)



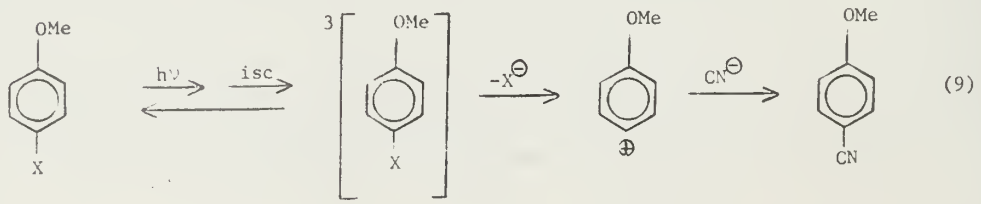
(7)



termination step (8)

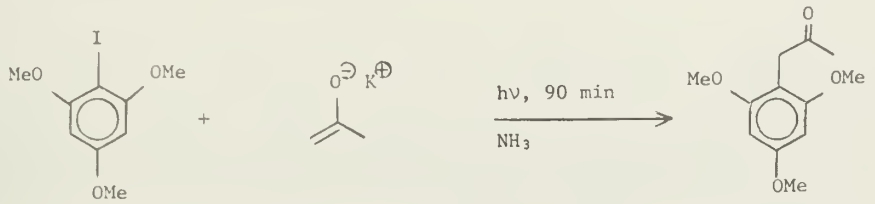
X = OMe or halogen

An alternate mechanism would be primary dissociation of the substrate to form the aromatic σ-cation, followed by addition of cyanide ion (equation 9).



(9)

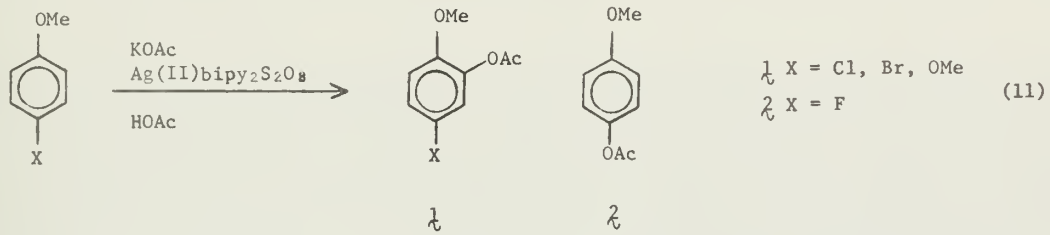
The strong preference for reaction with cyanide ion rather than with water (5000 times as reactive) provides contrary evidence however since aromatic σ-cations are thought to react indiscriminately with various nucleophiles.[9] In addition this scheme gives no provision for chain processes. In view of the factors favoring formation of radical cations, it appears likely that the photostimulated reaction of 2,4,6-trimethoxyiodobenzene with acetone enolate ion in liquid ammonia (equation 10), which Bennett and Sundberg list as an



(10)

example of the $S_{RN}1$ mechanism,[10] can be attributed to the $S_{ON}2$ mechanism.

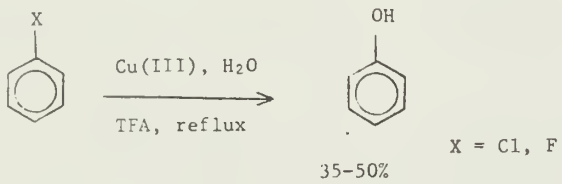
Metal ions provide another method of accomplishing the initial oxidation. Cobalt(III) as wolframocobalt(III)ate ion,[11] and the bipyridine complex of silver(II)[12] induce ipso substitution of 4-fluoroanisole by acetate at respective yields of 24% and 105% assuming 1:1 stoichiometry and with the metal ions as limiting reagents, though Ag(II) produced ortho substitution of the chloro and bromo compounds (equation 11).



(11)

1 2

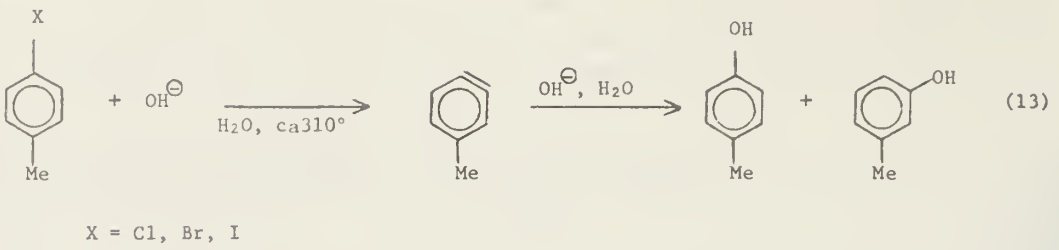
The copper (III) complex of biuret [potassium bis-(biuretato)cuprate(III)] promotes hydrolysis of fluoro- and chlorobenzene in trifluoroacetic acid (TFA) solution at reflux temperature[4] (equation 12), while this reaction does not



(12)

take place with only the much weaker oxidant, Cu(II), present.[13] Under these conditions 4-bromofluorobenzene gave a 10% yield of 4-bromo- and 4-fluorophenol in a ratio of 1.8:1, the same as was obtained anodically, 4-chlorofluorobenzene gave a 90% yield of 4-chloro- and 4-fluorophenol in a ratio of 1.7:1, and p-dichlorobenzene gave a 132% yield [based on Cu(III)] of 4-chlorophenol.[14]

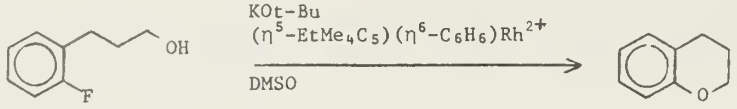
Eberhardt found that in acidic aqueous solution fluorobenzene is hydrolysed with a half-life less than 30 minutes at room temperature in the presence of sodium peroxydisulfate, Fe(II), and Cu(II), while in the absence of Cu(II) parahydroxylation was the predominant reaction.[15] Zoratti and Bunnett observed that while hydroxydehalogenation of 4-halotoluenes by hydroxide ion at temperatures near 310°C produces para and meta cresols in a ratio of 0.82 in the absence of oxygen and copper ions, consistent with an aryne mechanism (equation 13), air and traces of Cu(II) produced a switch to ipso hydroxydehalogenation.[16]



(13)

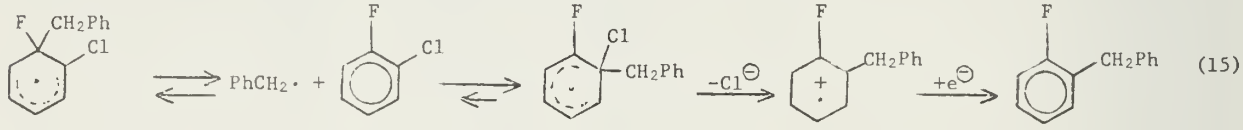
Sufficient Fe or Cd metals to keep nearly all copper reduced to metal suppressed ipso substitution. Britton claimed that copper metal must be electrolytically isolated from the iron walls of the vessel in industrial hydrolysis of chlorobenzene to be catalytically active.[17]

Houghton and Voyle have reported an intramolecular reaction similar to the intramolecular $S_{ON}i$ reaction, the Rh(III) catalyzed cyclization of 3-(O-fluorophenyl)propan-1-ol to form chroman[18] (equation 14).



(14)

An alternate entry into the $S_{ON}2$ mechanism involves nucleophilic radical attack upon the parent compound. In the reaction of cyclohexyl radicals with dihalobenzenes, Shelton and Uzelmeier observed that halogens are displaced in the sequence F>I>Br>Cl.[19] In contrast, Norhebel and coworkers found that benzyl radicals react with o-chlorofluorobenzene to give exclusively o-fluorodiphenylmethane with no trace of fluorine displacement.[20] The reversibility of the addition of the benzyl radical but not of cyclohexyl radical to the ipso positions would explain these results (equation 15).



(15)

In order to study attack by carboxylyl radicals, Eberson and Jönnson used benzoyloxyl radicals (from benzoyl peroxide) in a solution of 4-fluoroanisole and potassium acetate in glacial acetic acid.[21] The ratio of 4-methoxyphenyl acetate to benzoate of up to 10:1 indicated that a chain process had occurred, although the finding of Skell and May that at least two types of acetoxyl radicals exist,[22] the π-form of which is sufficiently stable to abstract H atoms, leaves it unclear whether the chain-propagating step involves oxidation of substrate or acetate.

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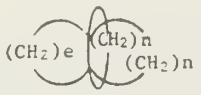
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SMALL RING PROPELLANES-BONDING & SYNTHESIS

Reported by Thomas C. Pochapsky January 31, 1983

I. Historical

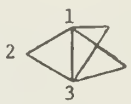
Since the geometry of tetravalent carbon was first established, organic chemists have been constantly attempting to defy nature by stretching, distorting and otherwise abusing the tetrahedron. Perhaps the most remarkable mayhem attempted thus far is to be found in the tricyclo[l.n.m.0]alkane or [l.n.m]propellane systems.[1] These compounds are characterized by three carbocycles fused at a common bond (I). In the small ring homologs of this



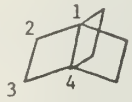
(I)



(II)



(III)



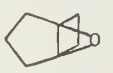
(IV)

series, the nominal T_d geometry of the bridgehead carbons is distorted to C_{3v} (trigonal-pyramidal) with central-side bond angles ϕ calculated to be 58.5° in [1.1.1]propellane (III),[2] and 87.4° in [2.2.2]propellane (IV).[3]

Besides posing interesting synthetic goals, the small-ring propellanes are of great theoretical interest as to the nature of the central bond. Various electronic calculations have predicted that as ring size decreases, electron density moves out from between the bridgehead carbons to the backside of the bridgehead.[4,5,6] In fact, total overlap population[7] was calculated to be negative for the (C_1-C_3) region of [1.1.1]propellane by SCF-CI *ab initio* calculations, implying a non-bonding or even an antibonding situation.[4]

There was, understandably, a certain amount of pessimism as to the ultimate stability of these compounds.[8] But undaunted experimentalists continued to work on the problem. Relatively unstrained larger members of the propellane series had been known for some time,[9] but the smaller ring compounds remained elusive.

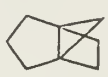
In 1967, Wiberg and co-workers, who have since been responsible for much of the experimental work in this field, succeeded in synthesizing an oxa-analog to [3.2.1]propellane, oxatricyclo[3.2.1.$0^{1,5}$]octane (V) by peracid oxidation of the corresponding bicycloalkene (VI).[10] Soon afterwards, Gassman obtained the parent carbocycle, [3.2.1]propellane (VII), from the same alkene by reaction with diazomethane.[11]



(V)



(VI)



(VII)

In 1972, Newton and Schulman published *ab initio* studies on [1.1.1]propellane and its parent bicyclo[1.1.1]pentane in which the unusual properties of the central bond were investigated.[4] Theoretical work by Hoffmann and Stohrer[5] introduced the possibility of "bond-stretch isomerism" in the [2.2.2]-propellane system, and also proposed an allowed pathway to the [2.2.2] system

involving intramolecular S_N2 displacement. Although the only successful scheme for the synthesis of the [2.2.2] system, that of 2(N,N Dimethylcarbamyl)-[2.2.2]propellane by Eaton and co-workers,[12] did not follow the Hoffmann pathway, many other successful syntheses did follow this path. These include the [3.1.1],[13] [2.2.1][14] and most recently, the [1.1.1] system synthesized by Wiberg and Walker.[15]

Other successful syntheses have been based on the addition of carbenes and carbenoid species to double bonds, forming a cyclopropyl ring, and in one case at least, a Diels-Alder addition.[16] The drawback to these pathways seems to be that one of the rings must be larger than four carbons, and the resulting propellanes, though certainly highly strained, are perhaps not as interesting to the purist, with the bridgehead bonds not restrained to one hemisphere.

II. Bonding and Electronic Structure

In order to discuss the nature of the central bond in small-ring propellanes, it is instructive to first look at a qualitative model of trigonal-pyramidal "methane" based on the extended Hückel (EHMO) method. Although the EH method does not provide accurate absolute energies or reliable bond length optimization, the dependence of the off diagonal H_{ij} elements in the Hückel determinant on the overlap integral provide a useful means of geometry opti-

$$(1) \quad H_{ij} = K'(S_{ij}) \qquad S_{ij} = \int \phi_1 \phi_2 d\Gamma$$

or

$$(2) \quad H_{ij} = .5K(H_{ii} + H_{jj})S_{ij}$$

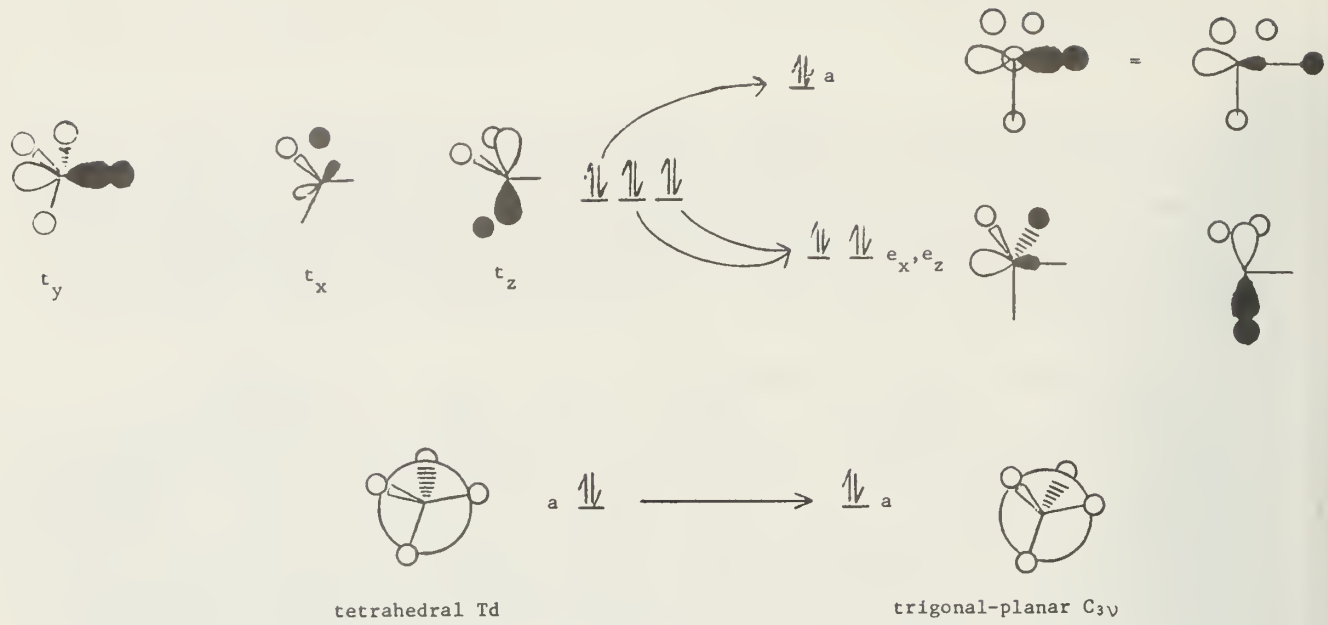
mization, as the S_{ij} integrals are dependent on internuclear distance.[17] For tetrahedral carbon, symmetry requires a completely symmetric $\underset{\sim}{a}$ MO (with largest Hückel co-efficients for C_{2s} and H_{1s}),[18,19] as well as 3 degenerate $\underset{\sim}{t}$ orbitals, each composed primarily of one carbon $\underset{\sim}{p_i}$ orbital and the H_{1s} orbitals overlapped in phase (Figure 1).

As the hydrogens are forced into a C_{3v} arrangement, the $\underset{\sim}{t_i}$ split to form two degenerate $\underset{\sim}{e}$ orbitals and a higher-energy $\underset{\sim}{a}$ orbital, which may be considered as "mixing in" the carbon $\underset{\sim}{2s}$ orbital.[19] The extent of overlap is not large [Hückel co-efficient ration $2S_c/2p_c = .18^5$] but enough to shift electron density to the backside of the carbon atom. The total destabilization involved in distorting methane from Td to C_{3v} is ca. 2.65 kcal/mole based on EH calculations.[5] This admittedly rough visualization is strengthened by <u>ab initio</u> calculations on the ethyl[20] and isopropyl[21] cations, which demonstrate the tendency of the carbon α to the positive charge to "flatten" towards trigonal pyrimidal with ϕ decreasing and hydrogens approaching planarity with the carbonium system (the "non-classical" carbonium ion.) The enlarged $\underset{\sim}{a}$ orbital lobe is stabilized by sharing electron density with the empty $\underset{\sim}{p}$ orbital on the cationic carbon.

Placed in the context of the [1.1.1]propellane system, this decrease in electron density in the direction of the bond along the C_3 axis, with a corresponding increase in density behind the bridgehead carbons, might be expected to greatly weaken the bridgehead-bridgehead bond. <u>Ab initio</u> calculations by Newton and Schulman[4] reinforced these suspicions. Using MBMO and EBMO basis sets, calculations were performed for [1.1.1]propellane and bicyclo[1.1.1]-pentane. In order to limit the number of variables, D_{3h} symmetry was assumed,

Figure 1.

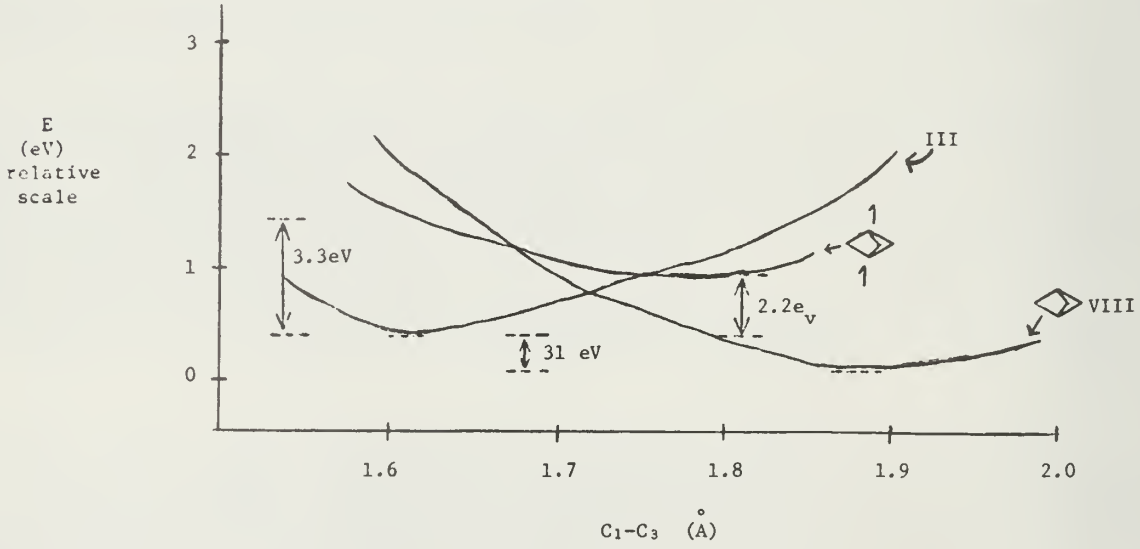
Representations of the t_i are not unique.



and bicyclobutane C-H bond lengths and HCH bond angles were used for the propellane. For the parent bicyclopentane, experimental values from electron diffraction studies were used (HCH - 104°[22], 1.545Å = C_1-C_2), again assuming D_{3h} symmetry.[23]

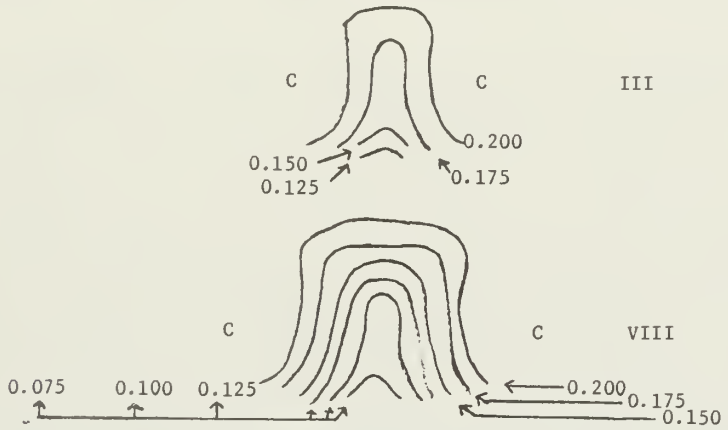
The results (Figure 2) indicate that an energy minimum exists for [1.1.1]-propellane (closed-shell singlet) with an equilibrium C_1-C_3 distance R = 1.60Å and a side bond R_{1-2} = 1.534Å. As 1.6Å is longer than the usual C-C bond, the possibility of a singlet diradical ground state was not ignored. Assuming

Figure 2.



the energy of the triplet was close in energy to that of the singlet, the easier triplet ab initio calculation was performed. At the propellane equilibrium distance, the triplet ground state was 3.3eV higher in energy than the closed-shell singlet. Optimization for the triplet state (1.80Å C_1-C_3) gave an energy still 2.2eV higher in energy than the optimum closed-shell singlet, leading to the conclusion that [1.1.1]propellane would indeed have a closed-shell singlet ground state.

Figure 3.



Although the calculation would seem to indicate a formal C_1-C_3 bond, total electron density mapping from the EBMO basis (Figure 3) shows a striking resemblance in the electron densities between C_1 and C_3 in both III (bonded C_1-C_3) and VIII (unbonded). Localization of the MBMO orbitals showed the central "bond" composed of $sp^{4.1}$ orbitals (ϕ = .44($2s_C$) + .89($2pz_C$)$_\bullet$) with the larger lobes pointing away from each other (Figure I). The C-C overlap population is -0.002 for the propellane C_1-C_3 "bonding" orbitals indicating a non-bonding or even slightly antibonding situation. Performing the same calculations with the nonlocalized EBMO orbitals gives total overlap populations as shown (Table I). Note that the total overlap in [1.1.1]propellane (C_1-C_3), though not as negative as in the bicyclo compound, compares closely with the "non-bonded" interactions of C_2-C_4.

Table I.

Total Overlap populations.

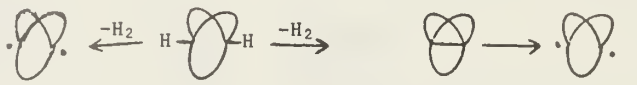
	C_2-H	C_1-C_3	C_1-C_2	C_2-C_4
[1.1.1]Propellane	.756	-.252	.346	-.285
bicycle[1.1.1]pentane	.784	-.908	.494	-.514

Why, then, is the closed-shell singlet an energy minimum? It would not suffice to say that localized orbital calculations are completely misleading in this case, as they allow accurate prediction of the reactivities of these species. However, it is the delocalized molecular orbitals which provide justification for III. 6-31G* ab initio calculations by Wiberg and co-workers[15] yielded approximate energies of dehydrogenation of the bicyclo parent compounds to both the diradical and closed-shell singlet species (Table II). Note that the strain energies of the propellanes remain constant (within an admittedly large range) depending on calculation method. However the strain energy of the related bicycloalkanes increases rapidly as ring size decreases, implying

that III is the most stable thermally and the least susceptible to free-radical polymerization in this series. These predictions, are for the most part, borne out.[15] The opening of IV to the diradical, though a forbidden reaction, is potentially exothermic.[5]

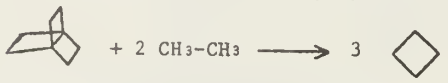
Table II.

(All energies in kcal/mole)



				Strain energies bicyclo	propellane
[2.2.2] (IV)	---	---	-1.4[C]	13[6]	90[A]
[2.2.1]	104	99	5	17[8]	85[8]
[2.1.1]	104	73	30	41.2[8]	90-100?[B]
[1.1.1] (III)	104	39	65	93.5[23]	105 110[4]

A) Strain energy for [2.2.2]propellane calculated from the hypothetical reaction



using SCF-CI energies for the propellane.

B) Estimated

C) A forbidden reaction, energy estimated from EH calculations[5] SCF-CI calculations[6] indicate this reaction is either thermoneutral or slightly endothermic.

The reason for the expected higher stability of III may lie partially in the fact that the parent VIII has an occupied a_2'' HOMO corresponding to the antisymmetric combination of the C-H bridgehead bonds (Figure 4), introducing a large degree of repulsion between C_1 and C_3 (HOMO overlap population = -.94, total = -.91). This leads to a net increase in intermethylene non-bonded re-

Figure 4.

HOMO in VIII.



pulsion. In III, the a_2'' orbital becomes the LUMO, and although anti-bonding interaction between C_1 and C_3 goes up slightly upon contraction of $R_{C_1-C_3}$ (overlap populations -0.14(1.8Å)→ -0.25(1.6Å)) the intermethylene antibonding overlap decreases dramatically (-1.66 → -0.86).

Then does a formal bond exist between C_1 and C_3 in III? Perhaps the question loses meaning in light of the evidence. That the molecule is relatively stable in a closed-shell singlet state is proven by its synthesis. The generation of the diradical is expected to be quite exothermic, and from *ab initio* calculations, the difference in strain energy between III and VIII parent bicycle is not very large, ca. 15 kcal/mole. It may be that systems with large numbers of nuclei constrained to a small volume of space are not modeled by maximum overlap methods (where only formally bonded atoms contribute S_{ij}) to any advantage.[4] (For perspective, a sphere described by the methylene carbon nuclei in III with R = 0.94Å would fit comfortably within the F^- ionic

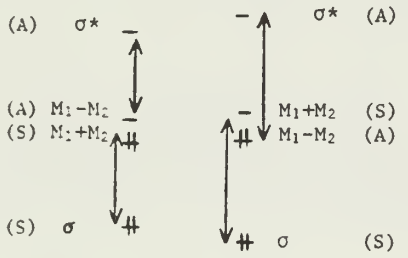
radius (1.3Å)). SCF calculations, with all overlaps considered, seem to be the best model. Though in the formal sense of the word, C_1 and C_3 may not be bonded, whole molecule considerations lower the energy of the symmetric HOMO, giving the closed-shell singlet.

That there is indeed strong interaction between the bridgehead carbons may be inferred from the large long-range coupling between the bridgehead protons in VIII (18Hz). INDO calculations show the coupling decreases monotonically with distance, suggesting direct rather than through side-bond interaction.[4]

The [2.2.2]propellane IV, which along with the [2.1.1] system represent the only propellanes not yet isolated as the pure hydrocarbons, poses less of a problem theoretically but a greater one synthetically. (Reports of the synthesis of the carbocycle IV by electroreduction of the 1,4 dibromobicyclo-[2.2.2]octane[24] could not be authenticated by isolation or spectroscopy.) Hoffmann[5] analyzed the [2.2.2]octane system by EH and qualitative MO theory. His results were reinforced by SCF-CI ab initio studies performed by Newton and Schulman.[6] By these studies, the [2.2.2] system would be expected to show "bond-stretch isomerism," that is, a double potential well is found as R_{1-4} is varied. This results from a level inversion between the symmetric and antisymmetric (with respect to the σ_n plane) combinations of the axial orbitals on C_1 and C_4 at the extremes of R_{1-4}. At the EH energy minimum for IV ($R \simeq 1.7$A) the symmetric ($m_1 + m_2$) combination is the HOMO, with SCF overlap of +0.64, denoting a relatively normal C_1-C_4 bond (C_1-C_2 and C_2-C_3 overlap populations are .68 and .70 respectively). At the extreme of the diradical (R_{1-4} = 2.55Å), with little C_1-C_4 interaction, the antisymmetric $m_1 - m_2$ combination is stabilized as shown in the correlation diagram (Figure 5) by interaction with the C_2-C_3 σ and σ^* levels.

Figure 5.

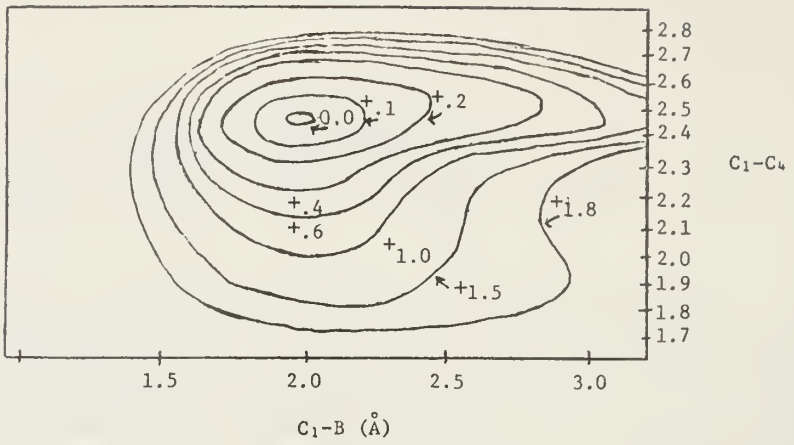
Note: only orbitals of like symmetry interact



Such stabilization would be expected to be most important for IV, with three σ bonds in the proper orientation for interaction, and to fall off as the number of carbons in the rings decreases. This is confirmed by calculation of the EH A vs. S energy levels for all the small ring propellanes. As mentioned earlier, the S combination is the HOMO for III at all internuclear distances. The [2.2.1]propellane is the only other system in which the A and S levels actually cross, and only at large R (R = 2.3Å). The conclusion is that the collapse of the diradical to form IV is a forbidden reaction, and bond stretch isomerism is possible. Unfortunately, the concerted 2s + 2s fragmentation of the diradical is allowed, and so the possibility of synthesizing IV via the diradical route seems poor.

A possible synthetic route is suggested, however, by the potential energy surface involving the approach of a Lewis acid (BH_3) along the internuclear axis C_3 of IV (Figure 6).

Figure 6.

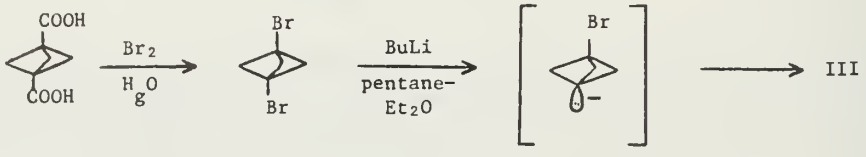


As the acid approaches, the energy of the HOMO is forced down while the LUMO of the BH_3 is forced up. At closest approach (R_{B-C_1} = 2.0Å) the zwitterion is formed at the low point of the potential surface. $R_{C_1-C_4}$ is about 2.4Å, near the equilibrium distance for the diradical. Noting the surface contours, it can be seen that the Lewis acid catalyses the interconversion of the diradical and the propellane. Reversal of zwitterion formation back to the propellane is of course an intramolecular S_N2 displacement, suggesting a possible synthetic route

The potential surface also indicates the sensitivity of small ring propellanes to electron acceptors, which might be expected considering the high electron density on the back side of the bridgeheads. Hoffmann further predicts by similar potential surfaces with Lewis bases that propellanes should be relatively inert to electron donors. The theoretical ease with which the diradicals form (Table II) indicates that propellanes should be fairly heat-sensitive and react quickly with radicals. All of these predictions have been borne out in practice.[11,14,15]

III. Synthesis

Several synthetic routes to highly strained propellanes are available, with intramolecular S_N2 displacement being used the most successfully. Wiberg's synthesis of III is instructive.[11]



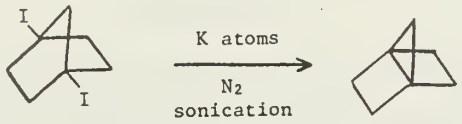
The thermal stability of III was great enough that the material could be purified by preparative GLC. At 114°C, the isolated product rearranged to methylenecyclobutane, and reacted with acetic acid to form 3-acetoxymethylenecyclobutane.



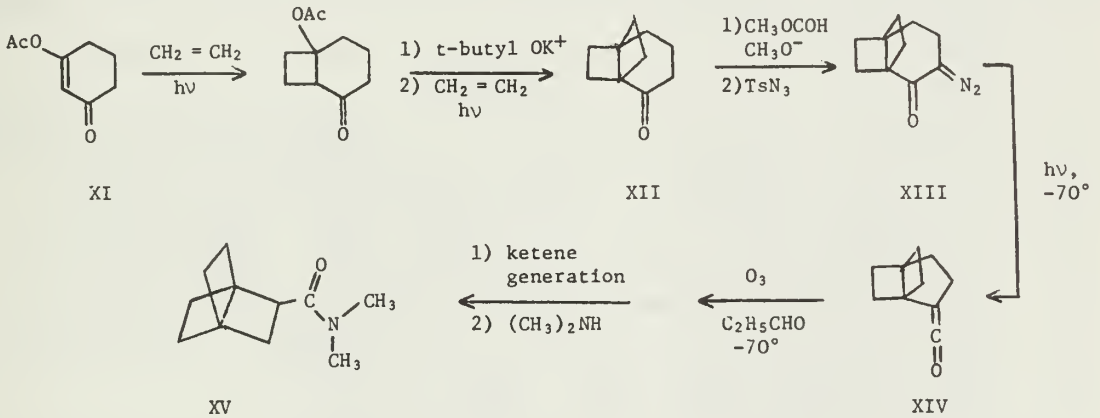
The same workers had earler tried to prepare [2.2.2]propellane (IV) by electroreduction of the 1,4 dibromide of IV.[24,25] No product was isolated, but introduction of Cl_2 to the system gave the 1,4 dichloride. As no polymerization was noted, this was taken as evidence of the formation of IV, as opposed to Cl_2 reaction with the diradical.



Wiberg has also synthesized the [2.2.1] system by gas phase dehalogenation of teh 1,3 diiodobycyclo[2.2.1]heptane.[14] A sonicated stream of alkali metal atoms in a N_2 matrix gas was used to accomplish the dehalogenation. The products were deposited on a cold CsI window and examined by FTIR. Spectral subtraction of norbornane (a minor product) gave a spectrum with a strong band at 530 cm^{-1}, which seems characteristic of the small ring propellanes.



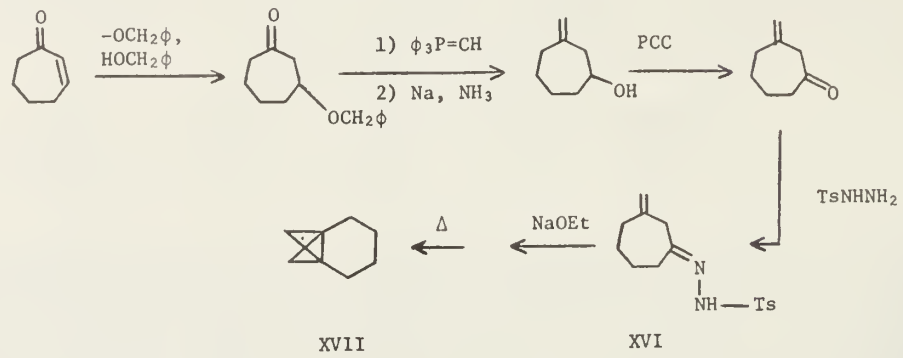
An alternative pathway is to form a less strained functionalized propellane system and then selectively remove carbon atoms from the ring. The only [2.2.2]propellane system isolated to date (that of 2(N,N dimethyl carbonyl) [2.2.2]propellane XV) by Eaton[12] has followed this route. The [4.2.2]propellane 2-one XII was generated by successive photoadditions of ethylene to the enol acetate XI. Formylation followed by reaction with tosyl azide gave the diazo compound XIII, which photo-rearranges to the ketene XIV. Ozonolysis gives a ketone with a ring one carbon smaller than XII. Repetition of the steps leading to the ketene followed by reaction of the ketene with dimethylamine affords CV, which was isolated by silica gel chromatography (-30°).



Thermal rearrangement gave 1,4 methylene products as predicted by Hoffmann. The relatively high activation energy of the rearrangement from rate studies (ca. 22 kcal/mole), also confirms the unallowedness of diradical formation from IV. The preceeding scheme of synthesis has also been used by Eaton for the preparation of the [4.2.2] and [3.2.2] hydrocarbons by Wolff-Kishner reduction of XII and [3.2.2]propellane2-one, respectively.[26]

Carbenoid insertion reactions represent the only other significant pathway for strained-ring propellane synthesis. Hamon and Trenerry[27] have syn-

thesized the [4.1.1]propellane following this route. Starting from 2,3 unsaturated cycloheptanone, XVI is generated. Thermal decomposition of the sodium salt of XVI, gives XVII, [4.1.1]propellane.



XVII XVI

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3. Calculated from EH energy minimum C_1-C_4 bond, 1.68Å. The (C_1-C_2), (C_2-C_3), (C_3-C_4) bond lengths were held constant at 1.54Å. SCF-CI calculations yielded bond lengths of 1.52A for the energy minimum, using the cyclobutane loond length (1.54Å) for the side bonds, giving a side-central bond angle of 90.4°. Ref. 5.
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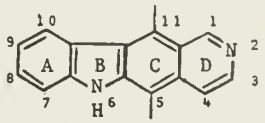
SYNTHETIC PATHWAYS TO ELLIPTICINE AND ITS DERIVATIVES

Reported by Ernest B. Clark February 3, 1983

Introduction. The alkaloid ellipticine (1) was first isolated from the species Ochrosia elliptica Labill. (family Apocynaceae) in 1958,[1] and subsequently from several other Apocynaceae genera.[2] A structure for this natural product was proposed by R. B. Woodward in 1959,[3] which his group supported by total synthesis from indole and 3-acetylpyridine. In 1962, Cranwell and Saxton[4] confirmed the structure by an alternate synthesis. Both syntheses afforded ellipticine in very low yield (1% or less from indole), and

Ellipticine

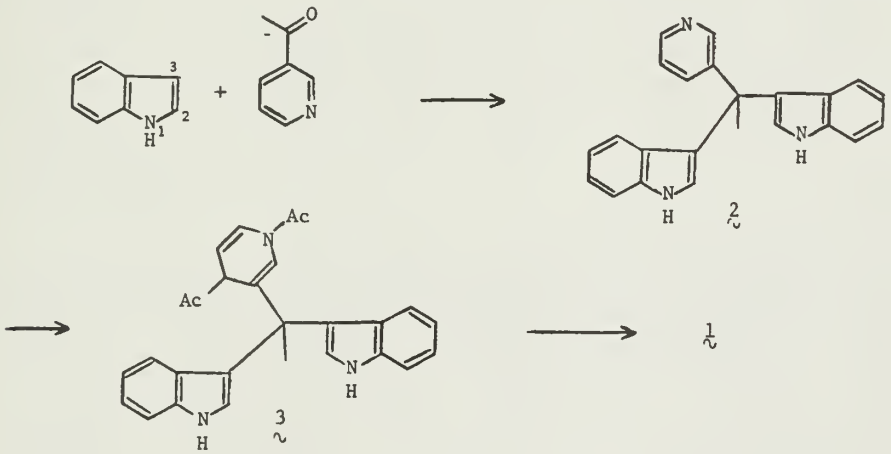
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interest in ellipticine chemistry languished until the discovery that ellipticine exhibited antitumor activity against a variety of human and animal systems[5] triggered intense synthetic interest in ellipticine and substituted ellipticines. Although literally dozens of syntheses of ellipticine and other 6H-pyrido[4,3-b]carbazoles have been reviewed in the literature,[2,6] none can be considered truly general; in fact, the ellipticine derivatives tested for pharmacological activity have been selected more by availability than by any rationale for testing ellipticine antitumor activity.[2] This abstract presents the procedures for ellipticine synthesis and their limitations.

Indole-Pyridine Syntheses of Ellipticine. Synthesis of the ellipticine ring system requires the creation of at least one of the rings ABCD of 1. Since the retrosynthetic destruction of ring C produces indole and pyridine units, many synthetic schemes have sought to form and then cyclize bridged indole-pyridine systems. Woodward's original synthesis[3] (Scheme I) followed this route. Indole was condensed with 3-acetylpyridine in acetic acid/zinc

Scheme I.

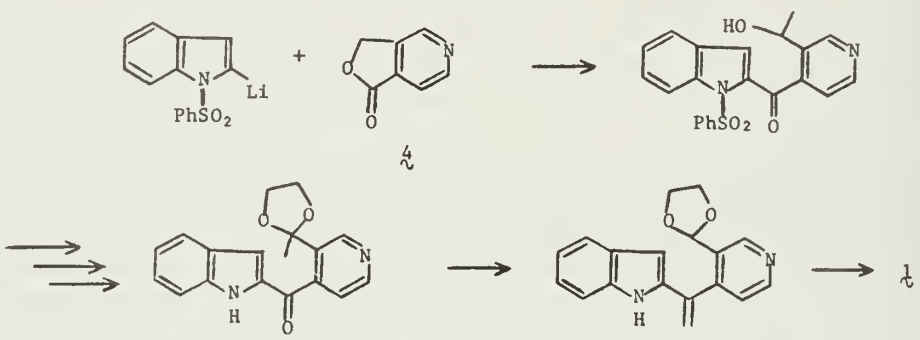


chloride to produce the bis-(3-indolyl) 2, which was diacetylated to 3 and pyrolyzed to produce ellipticine. A major difficulty with this procedure was that indole addition could not be halted at the 1:1 stage, and the pyrolysis

required to remove the second indole from the diacetylated 2:1 product produced ellipticine in only 2% yield. A modification of this procedure by Bergman and Carlsson[7] using 2-ethylindole instead of indole produced a 1:1 adduct which (after N-alkylation) cyclized in 72% yield, but careful control over pyrolytic conditions was necessary to prevent isomerization. Another pathway using 3-substituted pyridines was followed by Sainsbury and Schinazi,[8] who allowed indolylmagnesium bromide to react with 3-(1-chloro)ethylpyridine. After considerable further manipulation ellipticine was produced in 37% overall yield from 3-bromoindole.

Most of the indole-pyridine pathways to ellipticine link the two subunits together by a bridge attached gamma to the pyridine and adjacent to the indole nitrogen atoms. Kilminster and Sainsbury[9] formed such a bridge by condensing 3-(1-methoxyethyl)-4-acetylpyridine and the 1,3-diacetyl derivative of indolin-3-one in methanolic potassium hydroxide to produce (after four more steps) ellipticine in 29% yield from the indolinone derivative. A more popular way to form the aforementioned indole-pyridine bridged system has been by regiospecific lithiation of an N-arylsulfonyl indole followed by attack upon an appropriate functionalized pyridine such as 4-acetylpyridine,[10] isonicotinic anhydride,[11] 3,4-pyridine-dicarboxylic anhydride,[12] or the lactone 4[13] (Scheme II). The product from each of these additions must undergo considerable

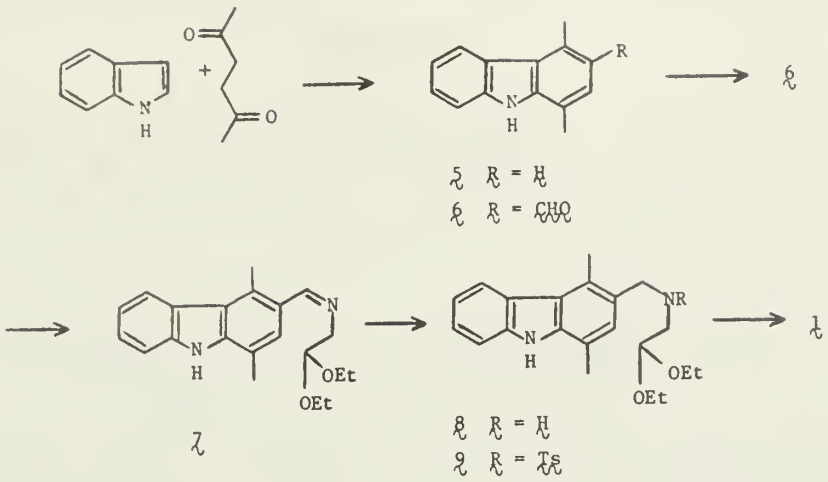
Scheme II.



extra manipulation before the final bond closing ring C can be formed; of these procedures, that of Saulnier and Gribble[12] produced the best overall yield of ellipticine (54% from indole). A related scheme by Watanabe and Snieckus[14] used an ingenious tandem metalation-addition sequence to form the ellipticine skeleton directly from indole-3-aldehydes and lithiated N,N-diethylisonicotamide. All these lithiation methods are limited in that ellipticine derivatives cannot be made which would require starting indoles or pyridines having substituents which would spoil the regiochemistry of the metalation.

Indole-Carbazole-Ellipticine Transformations. The first synthesis of ellipticine subsequent to the original work of Woodward was achieved by Cranwell and Saxton.[4] They formed the ABCD ellipticine ring system by starting with the indole AB structure and adding ring C and then D (Scheme III). They refluxed indole with 2,5-hexanedione in ethanolic hydrochloric acid, forming 1,4-dimethylcarbazole 5 in 36% yield, which they then formylated at the 3-position with phosphorus oxychloride and N-methylformanilide. Condensation of the resulting aldehyde 6 with 2,2-diethoxyethylamine gave the azomethine 7, which they attempted to transform directly into ellipticine using hot polyphosphoric acid according to the Pomeranz-Fritsch isoquinoline synthesis. When this experiment failed, they hydrogenated 7 to the amine 8 (R=H), which required sat-

Scheme III.



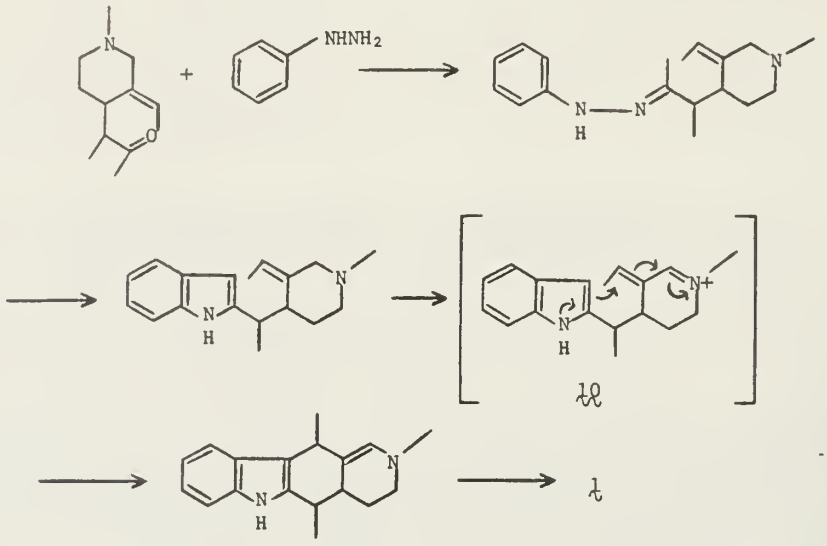
urated hydrogen chloride in ethanol for cyclization. Dehydrogenation of the product produced ellipticine in 1% yield from indole. More recent investigators have devoted considerable effort to improving the practicality of this procedure. Dalton[5] discovered that the failed Pomeranz-Fritsch cyclization of 7 was extremely sensitive to the water content of the phosphoric acid used. Ellipticine yield reached a maximum of 44% (7% overall from indole) in 98% phosphoric acid, dropping to very low when sufficient water was either added to produce 85% phosphoric acid or removed to produce a polyphosphoric acid. Not only did the elimination of the hydrogenation/dehydrogenation steps improve yield, but the less-vigorous cyclization conditions permitted the synthesis of several alkoxy-ellipticines. Jackson, Jenkins and Shannon[15] produced further improvement by treating 8 with tosyl chloride to produce tosylamide 9 (R=Ts), which cyclized directly to ellipticine in 8.3% yield from indole. All modifications of the Cranwell-Saxton procedure, however, encounter problems when many ellipticine derivatives are sought. Electron-donating or -withdrawing groups on ring A may prevent the closing of ring C to the carbazole, or may direct formylation such that isomers other than analogs of 6 are formed.[2]

Oikawa and Yonemitsu[16] used an indolyl-β-oxo-sulfoxide to form the ABC carbazole skeleton, which after D closure and dehydrogenation produced ellipticine in 23% yield. Besselievre and Husson[17] formed the carbazole skeleton (with a secondary amine side-chain) from indole and a substituted tetrahydropyridine ketal; a Mannich reaction closed the final ring and ellipticine was produced after dehydrogenation in 1% yield.

Fischer Indolization Routes. Several research groups have sought to form the B ring by assembling an arylhydrazone between the A-ring and the C- or D-ring, and then closing the B-ring by heating the hydrazone in acid by the Fischer indolization route. Langlois and Potier[18] formed ellipticine from phenylhydrazine and a highly-substituted tetrahydropyridine ketone (Scheme IV). Rings A and D were thus provided, and after the indolization the C ring was closed (by what the authors consider a potential biomimetic pathway via transition state 10) to afford ellipticine in 22% yield. One of the earliest ellipticine syntheses[19] followed a C + A → C-A → ABC → ABCD ring construction route by condensing 2-cyano-6-hydrazino-xylene with cyclohexanone and performing a Fischer indolization on the resulting hydrazone to get 7-cyano-1,2,3,4-tetrahydro-5,8-dimethylcarbazole. Dehydrogenation to the carbazole, conversion

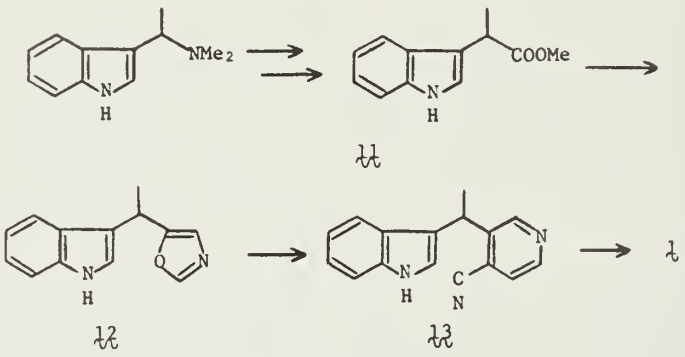
of the nitrile group into an aldehyde, a Bischler-Napieralsky cyclization and finally dehydrogenation produced ellipticine in minute yield.

Scheme IV.



Other Routes to Ellipticine. Kozikowski and Hasan[20] (Scheme V) started with the readily-available alkaloid gramine, elaborating it to produce the

Scheme V.



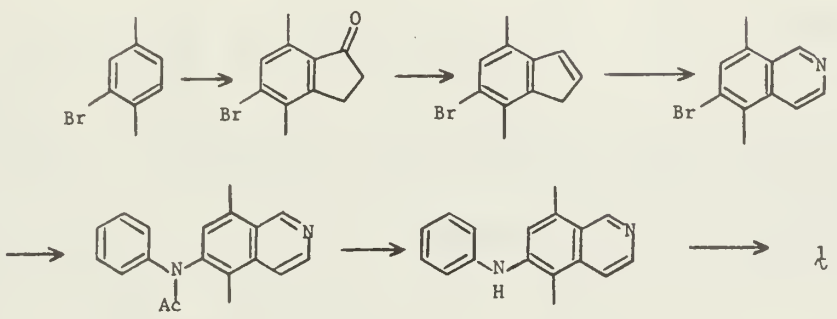
ester 11, which upon treatment with lithiated methylisocyanide produced oxazole 12. A diels-Alder addition of acrylonitrile produced 13, which Sainsbury and Schinazi[8] had earlier transformed into ellipticine. Although the formal yield from gramine is low (8%), the ease of adding substituents on the final C and D rings by varying the lithiated isocyanide and the dienophile makes this route an attractive choice for making 3- and 4-substituted ellipticines.

In the work of le Goffic, Gouyette and Ahond[21] methylgramine and a pyridone enamine are condensed, two missing carbons provided using an acetylide, and the resulting system dehydrogenated to ellipticine in 42% yield from the methylgramine.

The synthesis by Miller and Moock[22] (Scheme VI), starting with bromoxylene follows a C → CD → A-CD → ABCD ring elaboration to produce ellipticine. Bromoxylene is converted into 6-bromo-5,8-dimethylisoquinoline, which is coupled to acetanilide, deacetylated, and then cyclized to ellipticine using palladium

acetate in 20% yield from the bromoxylene. A variety of derivatives with A-ring substituents should be accessible by this procedure.

Scheme VI.



Preferred Synthetic Pathways. The surprising number and variety of ellipticine syntheses now available permit a reasonable choice of procedure to synthesize many ellipticine derivatives. If ellipticines having electron-donating groups in the 6-, 8-, 9-, or 8,9-positions are desired, some variant upon the Granwell-Saxton route through carbazoles is the most appropriate. Not only is the formylation to form an analog of 8 assisted, but occupying the 6- and 9-positions block those sites to undesired formylation there. Routes involving Fischer indolizations have been used to form 7- and 1-substituted ellipticines.[23,24] No serious efforts have been reported to synthesize 3-, 4-, or 10-substituted ellipticines, but the procedures of Miller and Moock could provide 10- derivatives, while the Kozikowski sequence using oxazole intermediates should provide ready access to the 3- and 4-ellipticines.

Antitumor Activity of Ellipticines. From the substituted ellipticines now available, a general consensus on the mechanism of ellipticine antitumor activity has been reached.[25] The planar, slightly curved ellipticine ring system slips well in between DNA base pairs, and this intercalation ruins DNA function, killing malignant cells preferentially. Substituents destroying planarity, such as 9-phenyl-, disrupt antitumor activity by preventing intercalation. In addition, the conjugate acids of ellipticines were found to be dozens of times more effective as intercalators than the uncharged species; substituents raising pK_6 to the point that protonation was negligible at physiological pH reduced activity. After over a decade of pharmacological tests of ellipticine derivatives, only 9-hydroxyellipticine (and its 2-methyl derivative) have been found to possess significantly greater antitumor activity than the naturally-occurring ellipticine and 9-methoxyellipticine; in fact, ellipticine is metabolized to 9-hydroxyellipticine in the rat.[6]

Summary. Dozens of routes are known to ellipticine and some derivatives, but all suffer from practical difficulty, be it low yield from available reagents, extensive manipulation to produce the ellipticine skeleton, or severe reaction conditions destructive to some desirable derivatives. The truly general synthesis of ellipticine and other 6H-pyrido[3,4b]carbazoles remains to be found.

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DIORGANYL DITELLURIDES: THEIR PHYSICAL PROPERTIES, SYNTHESIS, AND THE REACTIONS THEY UNDERGO

Reported by Kurt Kistler February 7, 1983

Introduction.

The purpose of this abstract is to present a general overview of the chemistry of diorganyl ditellurides,[1] and it shall be divided into three sections: I. Physical Properties of Diorganyl Ditellurides; II. Synthesis; and III. Reactions of Diorganyl Ditellurides. The term "diorganyl" shall be used to describe dialkyl and diaryl derivatives.

I. Physical Properties of Diorganyl Ditellurides

Dialkyl Ditellurides are viscous oils, orange to red in color, having a very foul and persistent odor among the lower numbers. They are much more unstable than their diaryl analogs, which are crystalline under atmospheric conditions.

The dihedral angles of diorganyl ditellurides have been predicted to be 75 - 80° by the extended Hückel method,[2] corresponding to the gauche conformation. These values were found to correlate well with those obtained from dipole moment measurements.[2,3]

It has also been determined by dipole moment data that the Te-Te bond is actually a multiple bond,[3] and has been described as a sigma bond plus a π_d-bond, which is thought to be a result of interaction between the lone pairs of electrons, possibly through d_{z^2} atomic orbitals. This inclusion of d-AOs of tellurium in the Te-Te bond, however, was found to overestimate the predicted dipole moment.[2] When calculations were made on dimethyl ditelluride with d-AO inclusion, a value of 2.07D was obtained; without d-AO inclusion the predicted value was 1.49D. The actual dipole moment of dimethyl ditelluride was found to be 1.53D,[7] which leads one to believe that d-AOs do not contribute in the occupied molecular orbitals of ditellurides.

The *trans* and *cis* rotational barriers were also calculated by the EHM without d-AOs to be 5.5 and 9.0 kcal/mole, respectively.[2]

The proton NMR for dimethyl dichalcogenides displays an interesting trend as one descends through this family.[5] The sulfur analog has a proton resonance at 2.38 ppm downfield from TMS. Dimethyl diselenide appears at 2.53 ppm, and the ditelluride has a resonance at 2.71 ppm. This proton dishielding trend is the opposite of what is observed in the monochalcogenides, which follow the usual inductive electronegativity effects. Although this problem has never been addressed directly, it could possibly be explained by anisotropy set up by the electrons forming bonds in addition to the central sigma bond. It can be imagined that as the heteroatoms become larger, this extra overlap will extend out farther, resulting in greater anisotropic effects in the induced magnetic field. This, however, is just conjecture.

Tellurium-125 NMR has been used to study organotellurium compounds. The ^{125}Te nucleas has a natural abundance of seven percent and a spin of ½, and so if a proton is two or three bonds removed from a tellurium atom, the PMR spec-

trum of that proton will be flanked by satellites with separation of $^{n}J(^{125}Te---H)(n = 2,3)$. Observation of the satellites and irradiation at 18.95 MHz gives ^{125}Te resonant frequencies. This double resonance, or "spin tickling," experiment was the first, though indirect, attempt at ^{125}Te-NMR. The technique used today entails proton decoupling of the tellurium resonances, and has been utilized successfully in the study of the diorganyl ditelluride exchange reaction, which is described in section III. A. of this abstract.

II. Synthesis of Diorganyl Ditellurides

The synthesis and isolation of diorganyl ditellurides has been confined to symmetric derivatives (Figure 1); no unsymmetric ditellurides have been stable enough to isolate (Figure 2).

Figure 1.

symmetric ditelluride

R-Te-Te-R

Figure 2.

unsymmetric ditelluride

R-Te-Te-R'

Dialkyl ditellurides have been synthesized by two general methods. Elemental tellurium powder can be reduced to sodium ditelluride by any of a number of reagents (eq. 1). The resulting dianion is then alkylated with two equivalents of an alkyl halide.

Equation 1.

$$Te(o) \xrightarrow[\substack{NaBH_4/EtOH/NaOH^{11} \\ Na/liq.\ NH_3{}^{12}}]{HOCH_2SO_2Na^{9,10}} Te^{-2} \xrightarrow[\substack{R = Me^{11,12,13} \\ Et^{10,13} \\ i\text{-}Pr^{11} \\ n\text{-}Bu^{10} \\ n\text{-}C_5H_{11}{}^{10} \\ CH_2Ph^{20,21}}]{2RX} R_2Te_2$$

Recently, Cava showed that alkyl telluride anions can be generated and air oxydized to the corresponding dialkyl ditelluride (eq. 2)[8] in approximately 85% yield.

Equation 2.

$$RLi + Te \xrightarrow{THF} RTeLi \xrightarrow{O_2} (RTe)_2$$

R = n-Bu, t-Bu

Dibenzl ditellurides can be formed by the method of eq. 1,[20,21] or by a technique by Cava[32] in which benzyl cyano tellurides are treated with aqueous hypophosphorous acid to give the dibenzyl ditelluride (eq. 3).

Equation 3.

$$Te(o) \xrightarrow[\substack{DMSO \\ 100°}]{KCN} KTeCN \xrightarrow[2)\ H_2O]{1)\ \phi CH_2Cl} \phi CH_2TeCN$$

61%

$$\xrightarrow[H_3PO_2]{50\%} (\phi CH_2)_2Te$$

91%

The general approach to diaryl ditellurides, by the method in eq. 2. requires the formation of the aryl tellurium anion as an intermediate, which is then air oxidized to the ditelluride. This anion can be the lithium anion or the magnesium bromide species (eq. 4).[15,16,17]

Equation 4.

$$\underset{(ArMgBr)}{ArLi} + Te \longrightarrow \underset{(ArTeMgBr)}{ArTeLi} \xrightarrow{O_2} Ar_2Te_2$$

In the case of the lithium species, it is important that the aryllithium reagent be generated by metallic lithium rather than n-BuLi, for the butyl halide formed in the latter case will alkylate the aryl telluride anion intermediate (eq. 5).[16]

Equation 5.

$$ArBr \xrightarrow{n\ BuLi} ArLi + n\text{-}BuBr$$

$$ArLi \xrightarrow{Te(o)} ArTeLi \xrightarrow{n\ BuBr} ArTe\text{-}n\text{-}Bu$$

It is possible to dealkylate the resulting telluride by refluxing with 48% HBr in acetic acid. This method has been used with the para-chloro-phenyl- and para-bromo-phenyl derivatives.[19]

Another procedure used to obtain diaryl ditellurides involves the reaction of tellurium tetrachloride with an appropriate arylating agent (eq. 6) to form the aryl tellurium trichloride, which can be reduced to the diaryl ditelluride.

Equation 6.

$$TeCl_4 \xrightarrow[\substack{ArH/AlCl_3[25] \\ SnAr_4[26] \\ PbAr_4[27,28] \\ ArHgCl[29]}]{ArH[22,23,24]} ArTeCl_3 \xrightarrow[\substack{Reduction= \\ Na_2S \cdot 9H_2O[30] \\ K_2S_2O_5[31]}]{reduction} Ar_2Te_2$$

III. Reactions of Diorganyl Ditellurides

There are two major types of reactions which diorganyl ditellurides undergo: those in which there is Te-Te bond cleavage, and those which result in Te-C cleavage with the extrusion of a tellurium atom.

1. Exchange Reaction of Diorganyl Ditellurides

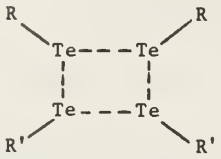
At room temperature it is possible to generate unsymmetrical ditellurides in situ by mixing a $CDCl_3$ solution of a symmetrical ditelluride with that of another symmetrical ditelluride. Such has been done with alkyl[33] and aryl[34] derivatives according to (eq. 7).

Equation 7.

$$\begin{matrix} R\text{-}Te\text{-}Te\text{-}R \\ + \\ R'\text{-}Te\text{-}Te\text{-}R' \end{matrix} \rightleftharpoons R\text{-}Te\text{-}Te\text{-}R'$$

These reactions have been monitored by ^{13}C-NMR[34b] and by ^{125}Te-NMR.[33,34a] Up until the early 1970's, it was believed that diorganyl ditellurides were partially dissociated into radicals in solution,[35] just as diorganyl disulfides are known to be.[36] However, vibrational spectroscopy,[37] Te-Möss-bauer spectroscopy,[38] and ESR[37] studies provide no evidence for this assumption. In addition, no reaction occurs between the radical trap triphenyl tin hydride and diaryl ditellurides at room temperature, though the exchange does take place.[38] At ∿80°, the rate of reaction to form $Ph_3SnTeAr$ was independent of the concentration of the ditelluride, depending only on the rate of decomposition of the triphenyl tin hydride. It has been postulated that the transition state of the exchange reaction is a dimer involving a four-membered Tellurium ring (Figure 3). The formation of it is slow and thermal in nature.[33,34,37,38]

Figure 3.



2. Reaction with Halogens

In general, diorganyl ditellurides react with halogens to form organyl tellurium trihalides (eq. 8).[39]

Equation 8.

$$R\text{-}Te\text{-}Te\text{-}R \xrightarrow{3X_2} 2\ R\text{-}TeX_3$$

X = Cl, Br, I; R = alkyl, p-$CH_3OC_6H_4$, p-$C_2H_5OC_6H_4$, p-$C_6H_5OC_6H_4$, p-$C_6H_5SC_6H_4$, O-$C_6H_5OC_6H_4$, 1-$C_{10}H_7$

An exception to this is the reaction of bis(2-naphthyl) ditelluride with excess iodine.[40] In this case, 2-naphthyl tellurenyl iodide is the product (eq. 9).

Equation 9.

$$(2\text{-}C_{10}H_7Te)_2 \xrightarrow{I_2} 2\text{-}C_{10}H_7TeI$$

Dibenzl ditelluride is another exception to this pattern. Reaction with less than one equivalent bromine extrudes Te and forms dibenzyl dibromo telluride, which is also the product of the dibenzyl telluride with bromine (eq. 10).[4] Excess bromination leads to tellurium tetrabromide plus benzyl bromide.

Equation 10.

$$\phi CH_2\text{-}Te\text{-}Te\text{-}CH_2\phi \xrightarrow{<1\text{eq } Br_2} \phi CH_2TeCH_2\phi \xrightarrow[Br_2]{\text{excess}} TeBr_4 + \phi CH_2Br$$

(Te; Br; Br)

$$\phi CH_2\text{-}Te\text{-}CH_2\phi \xrightarrow{<1\text{eq } Br_2}$$

Ditellurides are useful as dehalogenating agents. The reaction of vicinal dibromides and diaryl ditellurides at 110° yields the olefin, the diraryl tellurium dibromide, and tellurium (eq. 11).[41] Stereochemical examination shows that the reaction proceeds with trans elimination of the bromines.

Equation 11.

$$RCHBr\text{ —— }CHBrR \xrightarrow{Ar_2Te_2} RCH=CHR$$

Ar = p-MeO-C_6H_4, p-EtO-C_6H_4 R = C_6H_5, CO_2H

Even tellurium tetrahalides, aryl tellurium trichlorides, and diaryl selenium dibromides act as halogen donors toward diaryl ditellurides (eq. 12).[41] No mechanistic information has been published in regard to these reactions.

Equation 12.

$$TeX_4 \xrightarrow{2Ar_2Te_2} 2\ Ar_2TeX_2 + 3Te$$

$$2\ ArTeCl_3 \longrightarrow 3\ Ar_2TeCl_2 + 3Te$$

$$\phi_2SeBr_2 \xrightarrow{Ar_2Te_2} \phi_2Se + Ar_2TeBr_2 + Te$$

3. Thermolysis

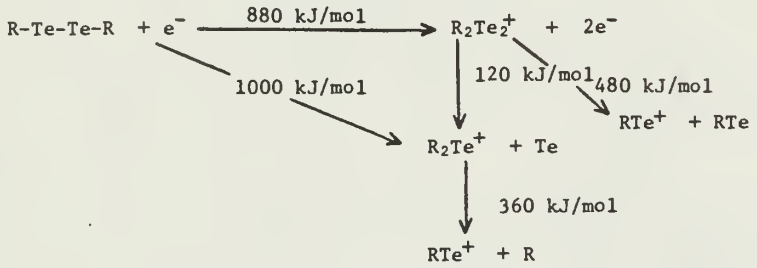
Diorganyl ditellurides, in general, when heated to above 120°, eliminate tellurium to form the corresponding diorganyl telluride (eq. 13).[35,42,43]

Equation 13.

$$R\text{-}Te\text{-}Te\text{-}R \xrightarrow{\Delta} R\text{-}Te\text{-}R + Te$$

Mass spectral data for diphenyl ditelluride[38] has shown that extrusion of Te from $R_2Te_2^+$ proceeds by a lower energy pathway than does Te-Te cleavage to form R-Te^+ from the parent ion. Figure 4 shows the decomposition paths with approximate energies associated with each.

Figure 4.



4. Reaction with Grignard Reagents

Ditellurides form unsymmetric tellurides in quantitative yield when treated with aromatic Grignard reagents (eq. 14).[42,44]

Equation 14.

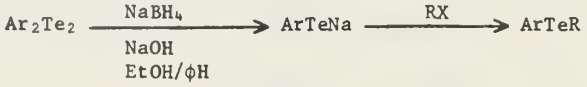
$$R_2Te_2 + ArMgX \longrightarrow R\text{-}Te\text{-}Ar + RTeMgX$$

Aliphatic Grignard reagents are inert to ditellurides,[44] but the telluride sought can be obtained by refluxing the ditelluride in dioxane with the appropriate dialkyl mercury compound.[45]

5. Formation of organyl telluride anions from ditellurides

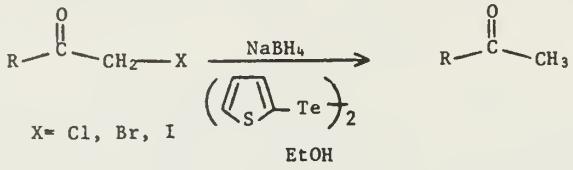
Lithium treatment of ether solution of diethyl ditelluride at room temperature yields Et-Te-Li.[46] The most common method to generate aryl telluride anions is to reduce the diaryl ditelluride with sodium borohydride in ethanolic benzene with sodium hydroxide present.[47] The resulting anion can be then trapped with an organic halide, as was done by Petrov in the reference cited (eq. 15).

Equation 15.



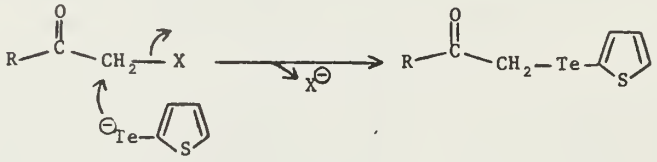
This reduction of ditellurides is fast compared to the reduction of carbonyls with sodium borohydride.[48] This fact has been exploited by Cava,[48] who recently showed that sodium borohydride added slowly under N_2 to an ethanolic solution of a α-halocarbonyl compound in the presence of a catalytic amount of bis(2-thienyl) ditelluride forms in good yield the parent carbonyl compound (eq. 16). Cava proposes a mechanism for this conversion. The ditelluride

Equation 16.



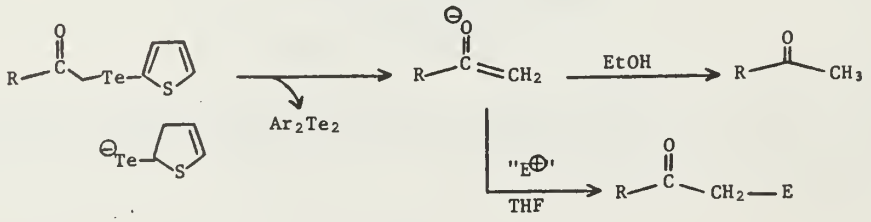
is reduced to two aryl telluride anions, one of which attachs the α-carbons and displaces the halogen (eq. 17). The resulting telluride is then attacked

Equation 17.



by the remaining aryl telluride anion, liberating the diaryl ditelluride and leaving the enolate, which can be protonated by ethanol, or alternatively trapped by an electrophile if the reaction is done in an aprotic medium (eq. 18).

Equation 18.



Alternatively, it is possible that the telluride anion attacks the α-substituent directly, forming the aryl tellurenyl halide and the enolate. This path has been postulated in similar selenolate reaction.[51]

Benzaldehyde has been used to trap the suspected enolate in dry THF in several cases.

6. Photolysis of dibenzyl ditelluride

Because the photolability of this compound is so extreme, this is the only ditelluride for which photolysis has had published results.[49] This compound rapidly forms dibenzyl telluride and tellurium under exposure to laboratory ceiling lights. Indeed, purification of the compound had to be carried out under red photographic safety lamps. In the presence of oxygen, a chloroform solution of dibenzyl ditelluride on photolysis afforded a mixture of benzaldehyde, benzyl alcohol, toluene, and 1,2 diphenyl ethane. It was proved that the dibenzyl telluride was the species oxidized photolytically and not the ditelluride. These results parallel those of dibenzl diselenide, for which a mechanism consistant with kinetic studies has been proposed.[50]

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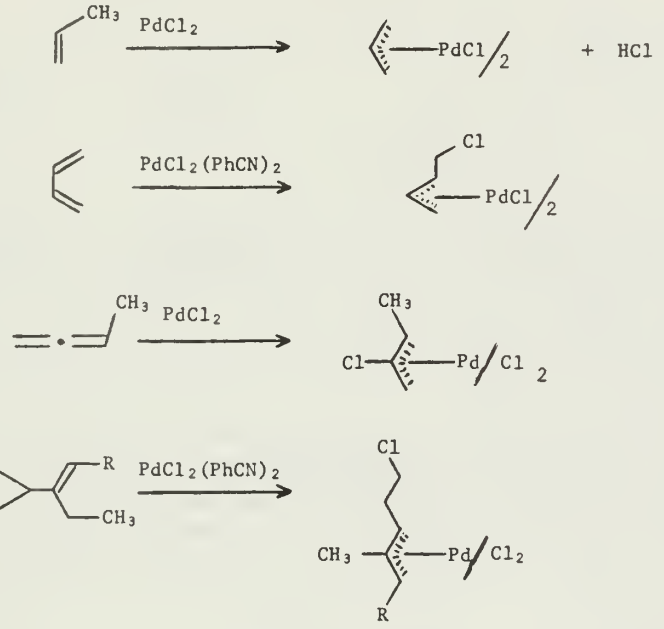
π-ALLYL PALLADIUM INTERMEDIATES IN CYCLIZATION

Reported by Chin-Wen Chen February 10, 1983

Introduction

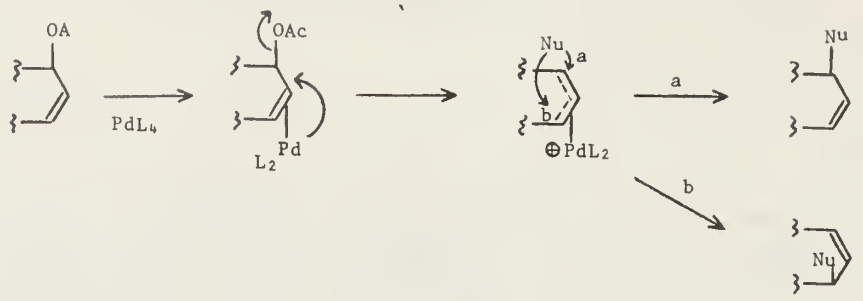
The use of palladium as a catalyst for synthetically useful reactions has increased in importance since the ingenious Wacker process was invented in 1958. In the Wacker process, acetaldehyde is produced on an industrial scale from ethylene by using $PdCl_2$ and $CuCl_2$ as catalysts. Palladium complexes are useful because they are stable under normal conditions and nontoxic as compared to other transition metal complexes. However, palladium is expensive and the complexes have high molecular weight; thus, the use of catalytic amounts of palladium is most desirable.

The use of π-allyl palladium complexes to promote carbon-carbon bond formation has been studied extensively and found to be of great synthetic value.[1] These complexes are stable compounds with three carbons coordinated to the metal symmetrically, and can be isolated and purified by chromatography or recrystallization. π-Allyl palladium complexes can be generated by addition of a palladium (II) salt to an olefin, diene, allene or vinyl cyclopropane. In these cases, stoichiometric amounts of palladium (II) salt are consumed and palladium (0) is produced when the complex reacts with nucleophiles.[1]



A more facile method of generation of π-allyl palladium moiety can be achieved by addition of catalytic amounts of palladium (0) complexes to an allylic ester, ether and even alcohol.[2] As illutstrated in Scheme I, in the first step of this reaction, it is assumed that palladium (0) coordinates to the olefin followed by palladium displacing the activated leaving group, such as acetate, from the opposite side. Now the π-allyl palladium can react with nucleophiles just the same manner as classical S_N2 displacement reactions. The nucleophiles attack from the opposite side with palladium serving as the leaving group. The configuration is retained in the overall reaction.[3]

Scheme I.

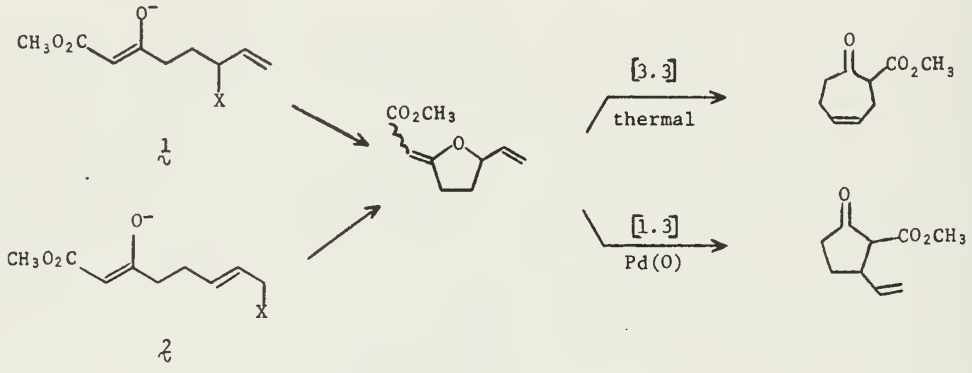


The development of π-allyl palladium intermediate in making carbon-carbon bonds provides a new methodology for making cyclic compounds. The scope of the use of π-allyl palladium intermediates in making cyclic compounds will be discussed in this report.

Formation of Cyclopentanoids

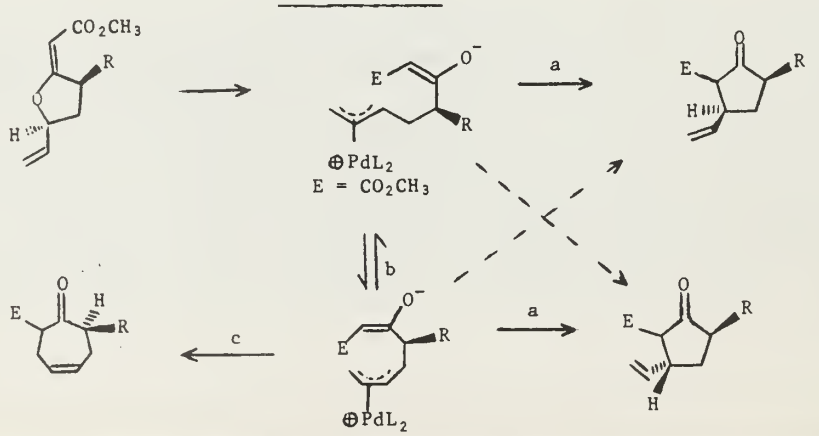
I. A 1,3-Oxygen to Carbon Shifts Approach.[4]

β-Ketoesters have played an important role in cyclization strategy. However, O- vs C-alkylation can diminish the yields of the cyclizations. This effect is particular notable in making five-membered-rings.[5] Attempts to cyclize 1 or 2 lead to O- rather than C-alkylated product.[5b]

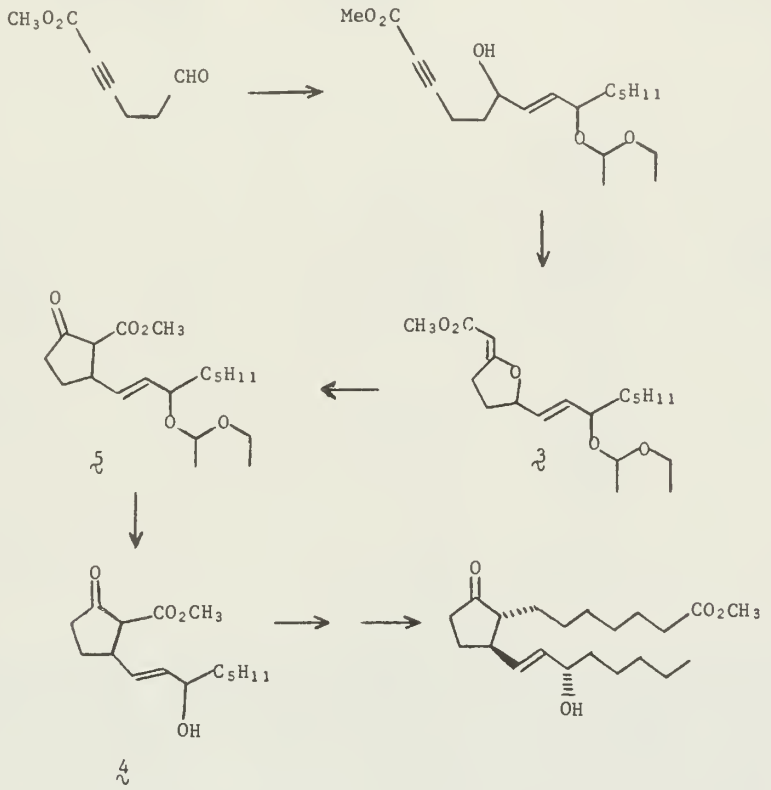


For systems with an vinyl substituent, the alkylidenetetrahydrofuran, can upon thermolysis produce cycloheptenone via a [3,3] sigmatropic rearrangement.[5] On the other hand, palladium (0) catalyst initiates ionization of the O-alkylated product to form a π-allyl palladium intermediate which can now undergo either ring closure (path a, scheme II) or syn-anti interconversion (path b in scheme II).[4a]

Scheme II.



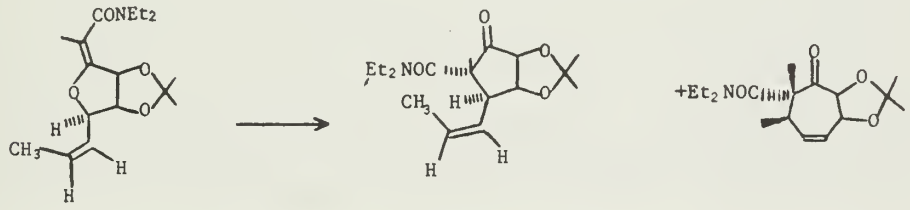
Synthesis of cyclopentanone 4[4b], a precursor to 11-deoxy-pGE[6], serves to illustrate the palladium (0) catalyzed rearrangement. Tetrahydrofuran 3, in the presence of O,N-bis(trimethylsilyl)-acetamide to prevent decarboxylation, was smoothly rearranged to cyclopentanoid. Removal of the protecting and the ethoxy-ethyl group with acetic acid in aqueous THF gave 4.



The rate of initiated ionization and the competition of syn-anti interconversion may result in a mixture of stereoisomers. These palladium catalyzed rearrangements are normally highly stereo specific and regio specific; these specificities are determined by the ligands and solvents used. Carbohydrate substrates 6 and 7 were used to study these solvent and ligand effects. The results are summarized in Table I and II. Using the bulkiest ligand, such as

Table I.

Pd-Catalyzed Rearrangement of 6.

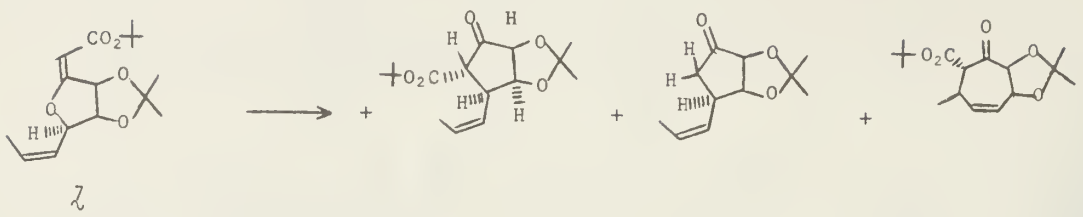


6

6% $(dppe)_2Pd$ DMSO	35	27
6% $(PPh_3)_4Pd$ DMSO	20	6 (73% of starting material recovered)
6% $(dppe)_2Pd$ Dioxane	93	

Table II.

Pd-Catalyzed Rearrangement of (E)-and (Z)-7



7

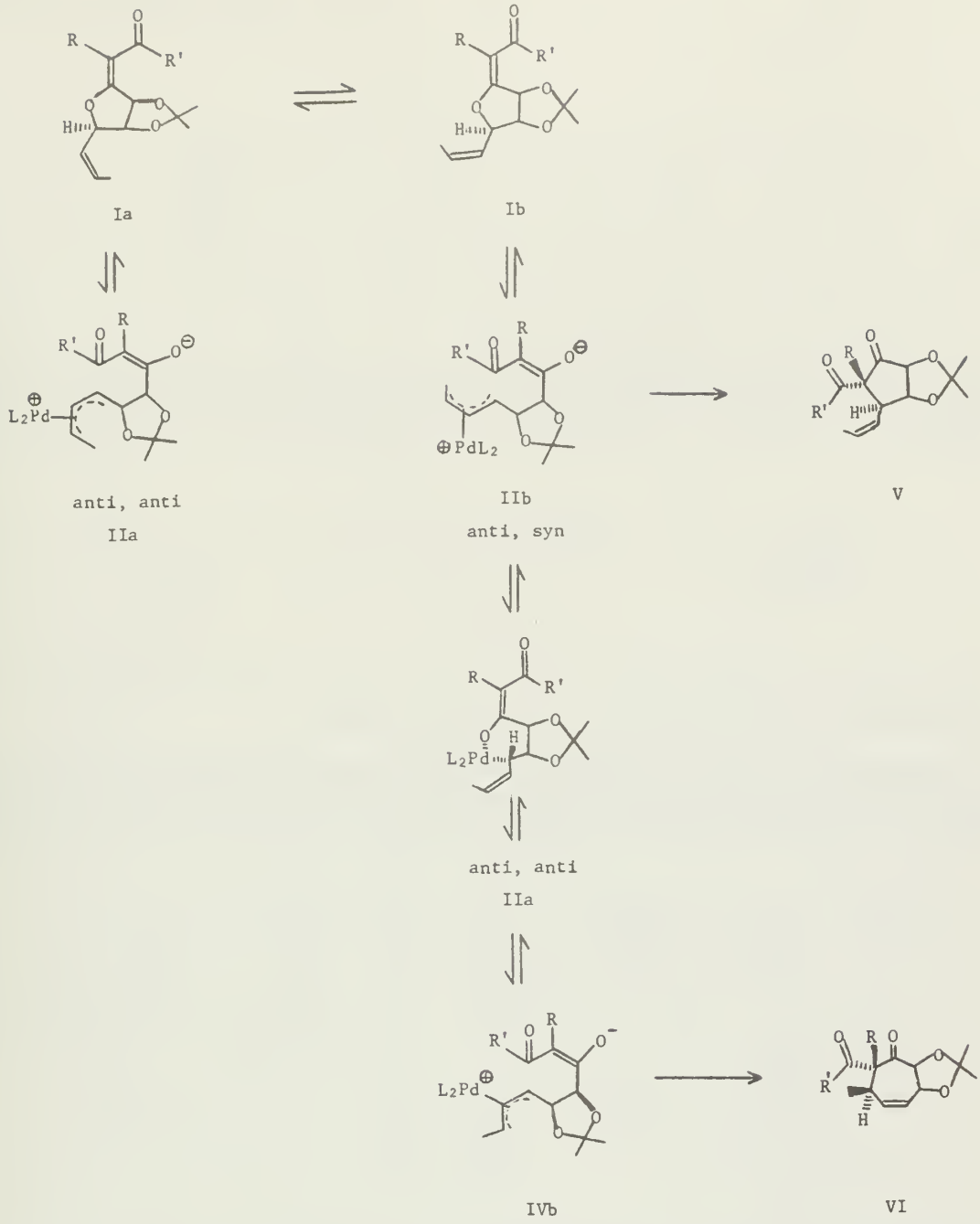
E	$(dppe)_2Pd$ DMSO			64
Z	$(PPh_3)_4Pd$ DMSO		35	50
E	$(PPh_3)_4Pd$ Dioxane	5	38	28
Z	PS-Pd Dioxane	11	75	5
E	PS-Pd O,N-bis Toluene	98		2
E	above, then DMSO		82	

polymer-supported catalyst, and toluene as solvent gave cyclopentanone exclusively. On the other hand, using the smallest ligand, 1,2-bis(diphenylphospho)-ethane (dppe) in DMSO gave only cycloheptenone. Scheme III presents the overall picture which rationalizes these results. Ionization occurs preferentially from the conformer I_b rather than I_a in order to avoid the unfavorable anti-anti π-allyl complex II_a.[7] Formation of cyclopentanones occurs directly from anti, syn complex II_b. Formation of a cycloheptenone from II_b is precluded because such a reaction requires creation of a trans double bond in a seven member ring. However, due to the steric hindrance created by the acetonide group, the rate of ring closure to form cyclopentanone is slowed down. Thus, in this case, syn-anti interconversion proceeds through σ-bonded intermediates and leads to syn-anti complex IV_b ultimately. Formation of seven-membered-ring arises from the syn-anti intermediate IV_b. Thus, the effects of the change of ligands and solvents on the ratio of five- to seven-membered-ring arise from the effect of changes on the rate of cyclization to cyclopentanone compared to the rate of syn-anti interconversion. Since DMSO can act as an extra ligand in the σ-bonded intermediates, DMSO enhanced the rate of syn-anti interconversion.[8] Also bulky groups such as triphenylphosphine and polymer supported catalysts inhibit the formation of σ-complexes and decrease the rate of syn-anti interconversion. Thus, the use of the bulkiest ligand, polymer-supported pallidium catalyst in toluene, formed cyclopentanone exclusively. On the other hand, using $Pd(dppe)_2$ as a catalyst in DMSO gave only cycloheptenone. The palladium catalyzed rearrangement of cycloheptenone provides a milder equivalent route to a [3,3]claisen rearrangement.

II. A [3+2] approach.[9]

The Diels-Alder [4+2] cycloaddition offers a powerful way to construct cyclohexenes. However, its analogue, a [3+2] cycloaddition strategy to reach carbocyclic five-membered-rings has seen little use. Although 1,3 dipolar cyclo-

Scheme III.



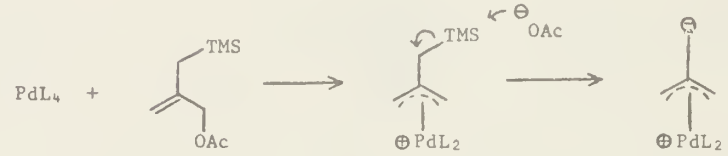
additions for heterocyclic have been well documented in organic chemistry, its carbon analogues for such cyclization have not been available.

Trimethylenemethane (TMM) 8, however, is attractive to this strategy.[10] Its absence as a synthetic method stems from the lack of a suitable method to generate it and the low yields in its cycloadditions.[11]



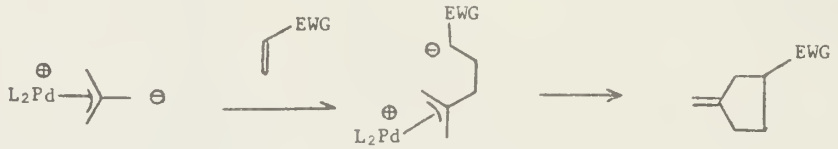
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Palladium (0) induced ionization of substrate 9, followed by desilylation offers a mild way to generate TMM-Pd complex 10 which could be equivalent to TMM. Reaction of the intermediate 10 with an electron deficient double-



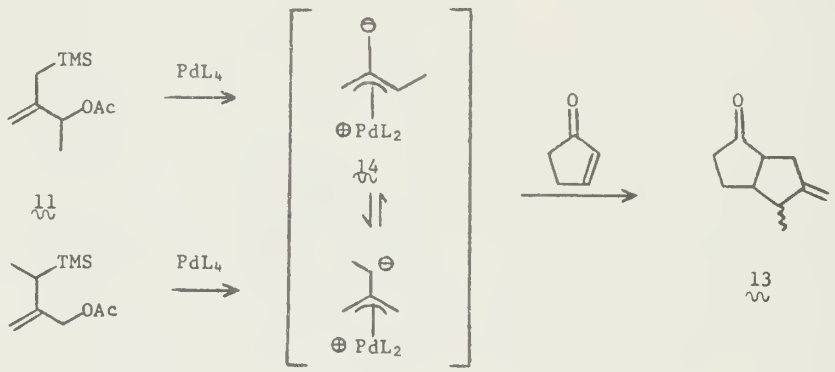
9 10

bond gives an alkylidenecyclopentanoid. This reaction involves a two-step process: conjugative addition of the negative end of the TMM-Pd complex onto the dienophile followed by nucleophilic displacement on the π-allyl palladium complex with the palladium serving as the leaving group. The degree of stereo-



selectivity usually depends on the rate of ring closure relative to the bond rotations; the stereoselectivity is quite high.

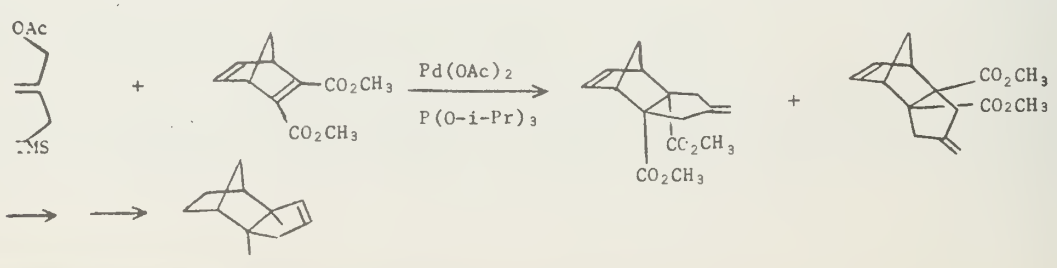
Reactions of 11 and 12 with cyclopentenone give only the regioisomer, 13, which is obviously derived from 15. Molecular orbital calculations suggest



11 12 15

that 15 may be more stable than 14.[12] Thus, in contrast to normal expectations, the electron releasing group prefers to be on the most electron rich carbon of the TMM-Pd complex. Such a perturbation of normal organic reactivity clearly is to be attributed to the transition metal.

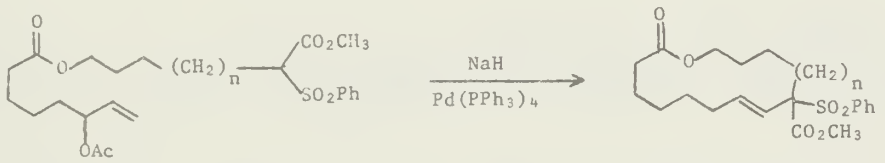
As an illustration of synthetic usefulness, (±)-albene 16 was synthesized.[13]



16

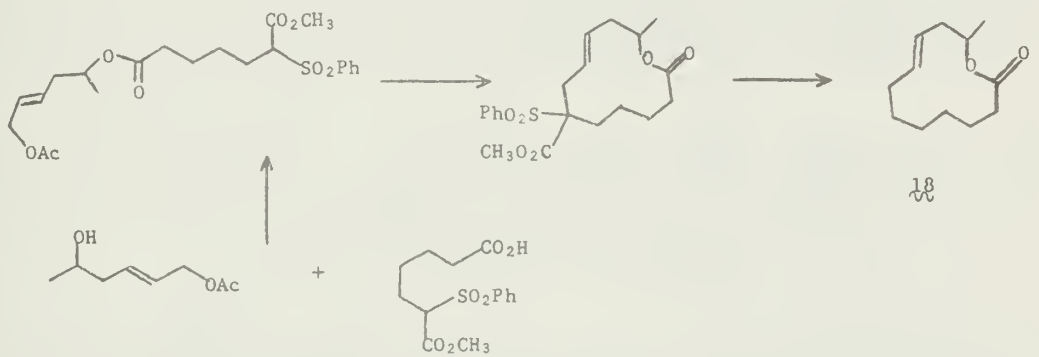
A Macrolides Approach.[14]

Synthesis of macrolides has been focused on lactonization of bifunctional acyclic precursors.[15] Creation of macrolides by intramolecular carbon-carbon bond formation is unusual. Directed Aldol cyclization by using activated zinc and diethyl aluminium chloride[16] intramolecular Diels-Alder reactions,[17] Claisen rearrangement[18] or oxidative coupling of α,ω-diacetylene[19] have been reported. However, the preparations of lactones via carbon-carbon bond formation provide a more flexible method in synthesis design than conventional routes. Also, a convergent synthetic scheme can be designed; acid and alcohol portions of the precursor can be synthesized independently then readily condensed to form ester prior to ring closure. Addition of the anion of 16 to a refluxing THF solution containing catalytic amounts of tetrakis(triphenylphosphine)palladium catalysts gives the desired macrolide 17 in good yield. In addition to high yield, only trans-double bonds were observed. In order to define the regio and stereochem-



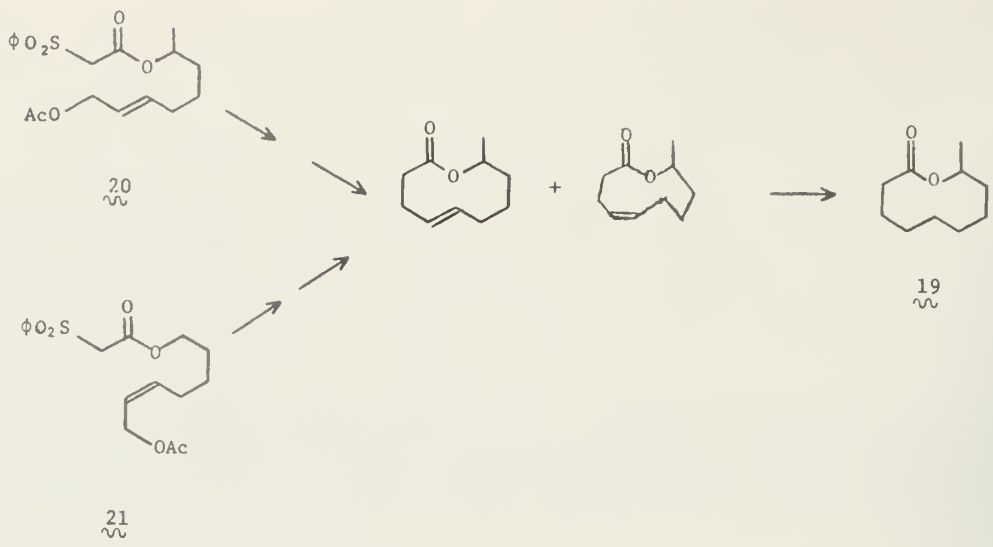
16 17

istry of this type of reaction, (±) recifeiolide 18 and (±) phoracantholide I 19, naturally occurring twelve- and ten-membered-ring macrolides respectively, were synthesized from their acyclic precursors. In the case of the twelve mem-



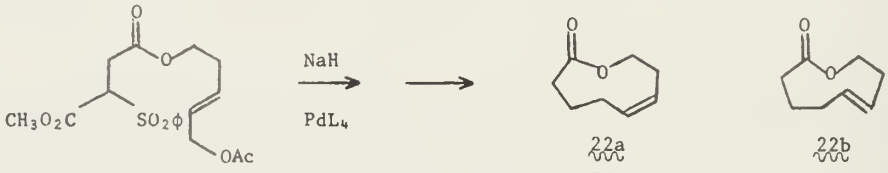
18

bered ring, only 18 was isolated, in 78% yield, with trans double bond only. In the case of the ten-membered-ring, cyclization of 20 and 21 respectively under the same conditions gave only ten-membered-ring products. However, the stereo specificity of the olefin is lost somewhat. From the trans acyclic precursor 20, the ratio of (E)- and (Z)- isomers is 88:12. From the cis acyclic precursor 21, the ratio is 65:35. 22a and 22b, nine-membered-ring macrolides, were prepared from 23 under the same conditions mentioned above giving only 29% yield with 76:24 ratio of (Z)- and (E)- isomers. However, the yield was increased to 60% and ratio of (Z)- and (E)- isomers became 91:9 when the reaction was done in the presence of 1.2-bis-(diphenylphospho)ethane. Cyclization of 24 with $Pd(dppe)_2$ as the catalyst gave the heptanolides 25 in 73% yield with only trace amounts of 26.



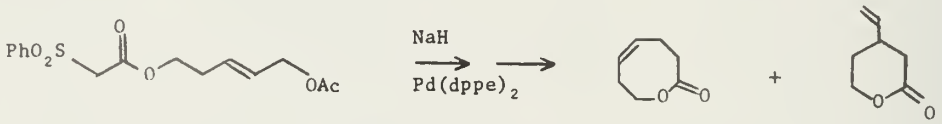
20 19 21

Noteworthy in these cases, both sides of the π-allyl palladium intermediate can be attacked by the nucleophiles. Attack on primary carbon is ap-



	22a	22b
L = $P\phi_3$ (29%)	76	24
L = dppe (60%)	91	9

parently kinetically more favorable than attack on secondary carbon. Rates of the closures of large size rings (greater than ten-membered-ring) are not that much different.[20] Thus, only one regioisomer can be expected from the attack



24 25 26

at the primary carbon. The rate of intramolecular displacement reactions in cyclization of six- and seven- membered rings are 10^3- 10^4 times faster than the cyclization of eight- and nine-membered rings.[20] However, only the regioisomers resulting from attack at the primary carbon were observed. The reasons for the preference for the formation of eight-membered-rings and nine-membered-rings over six-membered-ring and seven membered-rings in these palladium catalyzed reactions are not clear.

In this methodology, formations of medium size macrolides are obviously not so satisfactory as formation of large size macrolides. This method, however, provides a complementary method for conventional lactonization methodology especially in making medium size macrolides which are not easily achieved via conventional lactonization methods.[21] In all cases, no dimeric products were observed. This fact is attributed to the negatively charged nucleophiles preventing other negatively charged nucleophiles from intermolecular attack.[22]

Electrophiles are absent until activation by palladium, and only catalytic amounts of palladium (0) are used; thus a high-dilution effect is achieved.

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SELECTIVE PERFLUOROALKYLATION METHODS

Reported by Charles F. Kahle II February 14, 1983

Much of the interest in perfluoroalkylation methods has arisen from the discovery that many fluorine containing compounds are biologically active.[1] The desire to transfer perfluoroalkyl units into selected positions of a preexisting carbon skeleton has resulted in the development of radical, nucleophilic and electrophilic methods of perfluoroalkylation. This paper will focus attention on the more recent advances in these areas.

Methods of transferring perfluoroalkyl units into organic molecules are not only of biological interest but also represent a unique challenge in organic synthesis. The nature of perfluoroalkyl groups causes conventional alkylation reactions such as Grignard reactions, the use of organolithiums and Friedel-Crafts alkylation reactions to be impractical.[2,3]

Substitution of fluorine for hydrogen in an alkyl group strongly influences the behavior of an adjacent reaction center. The high effective nuclear charge of fluorine makes it the most electronegative element. The sigma inductive constant, σ_I, values for Cl (σ_I=0.47), F (σ_I=0.52) and CN (σ_I=0.58) show F to be intermediate between Cl and CN in inductive electron withdrawing ability.[4]

Perfluoroalkanes are inert to hydrolysis at temperatures below 500°C.[5] However, they are calculated to be thermodynamically unstable to hydrolysis. For example, the hydrolysis of CF_4 is exothermic by 72.8 kcal/mol. The stability of CF_4 is explained

$$CF_4 + 2H_2O \longrightarrow 4HF + CO_2 \qquad -72 \text{ kcal/mol}$$

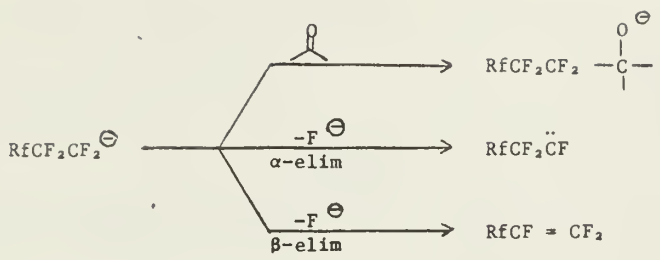
kinetically as a high activation energy for hydrolysis. The C-F bond is short (1.32A°) and difficult to polarize. The F atoms shield the carbon skeleton.

Despite large differences in reactivity a fluorine atom and hydrogen atom are very similar in size. Fluorine has a Van der Waals radius of 1.35Å and that for hydrogen is 1.10Å. In fact, substitution of H by F has been previously described as an "isogeometric transformation".[6] Chlorine is much larger with a radius of 1.80Å.

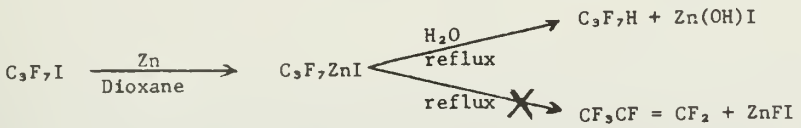
Perfluorocarbanions as reactive intermediates

Perfluorocarbanions are stabilized by the inductive electron withdrawing effect of the fluorine atoms. Unfortunately instead of reacting with an electrophile they may also decompose by α- or β-fluoride elimination (Scheme I).

Scheme I



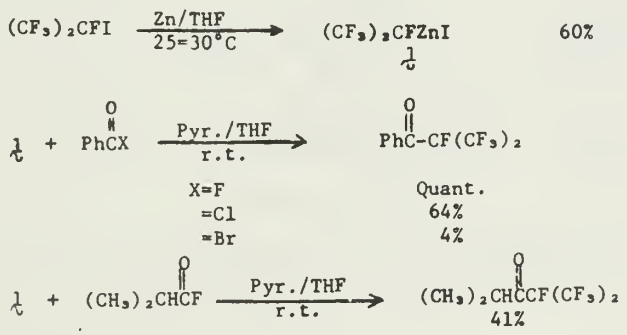
Perfluoroalkyl organometallics such as Grignards and organolithiums are stable only at low temperatures (-78°C) and readily decompose at room temperature.[2] This instability severely limits their synthetic utility, so they will not be discussed here. In contrast, perfluoro-n-propyl[7] and perfluoroisopropyl zinc iodide[2] have been prepared and shown to be thermally stable in solution. The perfluoropropyl zinc iodides were prepared by the reaction of perfluoropropyl iodide with zinc dust in dioxane at room temperature (Eqn.1). Perfluoropropene was isolated as a side product in both cases.



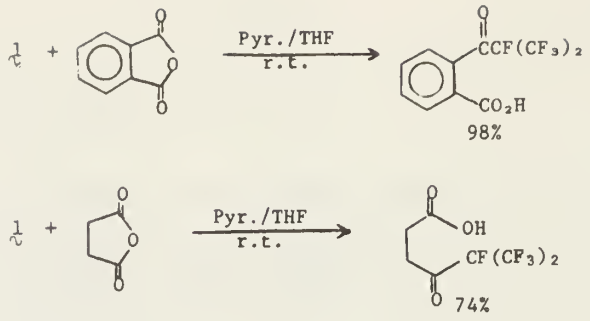
(1)

Yields of 50-60% of perfluoro-n-propyl zinc iodide were determined by hydrolysis and recovery of the 1-H-heptafluoropropane. Perfluoro-isopropyl zinc iodide is prepared in the same manner in 47% yield, as determined by isolation of 2-H-heptafluoropropane after hydrolysis. All attempts to make trifluoromethyl zinc iodide and pentafluoroethyl zinc iodide under similar conditions were unsuccessful. In dioxane solution both prefluoro-n-propyl and perfluoroisopropyl zinc iodide are unreactive toward organic electrophiles such as aldehydes, ketones, anhydrides and acid halides.

It was later found by Ishikawa, et al.,[8] that reaction of perfluoro-isopropyl zinc iodide 1 could be induced in high yields with acid fluorides and anhydrides in the presence of pyridine (Eqn. 2). No reaction was observed when triethylamine, N-methyl piperidine or N,N-dimethyl aniline was used in place of pyridine.

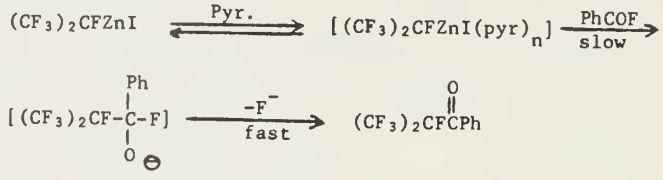


(2)



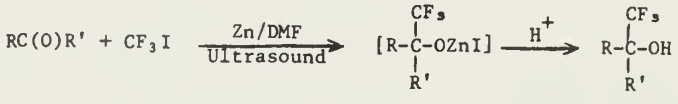
(2)

Ishikawa postulates that these reactions (Eqn. 2) occur through an addition - elimination mechanism in which the pyridine accelerates the addition step by coordinating to the zinc atom (Eqn. 3).



(3)

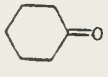
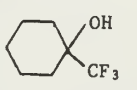
In 1981 Ishikawa, et al., found that irradiation with ultrasound[9] (35W, 32KHz) of a DMF solution of trifluoromethyl iodide, Zn powder and a variety of carbonyl compounds he could obtain smooth reaction to give the α-trifluoromethyl carbinols in good yields (Eqn. 4).[10] Trifluoromethyl iodide did not react with Zn dust in DMF without the aid of the ultrasound. The intermediate trifluoromethyl zinc iodide has not been isolated or observed spectroscopically.



(4)

Some of the products and their yields using this method are shown in Table I.

Table I

Carbonyl	Product	Yield (%)
PhCHO	$PhCH(CF_3)OH$	72
		48
MeCH=CHCHO	$MeCH=CHCH(CF_3)OH$	62
PhCOMe	$PhC(CF_3)(Me)OH$	55

An alternative method for the trifluoromethylation of carbonyl compounds was recently published by Meijere and coworkers.[11] It is reported that the trifluoromethylating reagent trimethylsilyl (trifluoromethyl) diazene 3 could be generated from THF solution of trifluoronitroso methane and lithium bis (trimethylsilyl) amide 2 at -80°C (Eqn. 5).

$$CF_3NO + LiN(SiMe_3)_2 \xrightarrow[-80°C]{THF} CF_3-N=N-SiMe_3 \qquad (5)$$

Meijere generated 3 in the presence of cyclohexanone or trifluoroacetophenone at -100°C and recovered 30% and 34% respectively of the α-trifluoromethyl carbinols (Eqn. 6).

$$R^1\overset{O}{\overset{\|}{C}}R^2 \xrightarrow[NaN(SiMe_3)_2]{CF_3NO/THF/-100°C} \underset{R^1}{\overset{HO}{\times}}\underset{R^2}{\overset{CF_3}{\times}} \qquad (6)$$

R^1 = Ph, R = CF_3 — 34%

R^1, R^2 = $-(CH_3)_5-$ — 30%

Ishikawa has also made use of perfluoroalkyl tin (IV) halides 4 as nucleophilic perfluoroalkylating reagents.[12] The perfluoroalkyl tin (IV) halides were prepared by oxidative addition of stannous chloride or stannous fluoride to perfluoroalkyl iodides (Eqn. 7).

$$RfI + SnX_2 \xrightarrow[r.t.]{DMF} RfSnX_2I \qquad (7)$$

(X = Cl or F, Rf = CF_3, n-C_3F_7, i-C_3F_7)

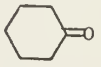
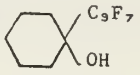
Ishikawa could not isolate compounds 4 but could observe them by ^{19}F NMR. The ^{19}F NMR spectrum of CF_3SnCL_2I in DMF had a singlet at δ-67.0 and that of CF_3SnF_2I had singlets at δ-65.0 and δ-25.5 in the ratio 3:2 respectively.[13]

As in the case of the perfluoroalkyl zinc iodides, pyridine catalyzes the reactions of the perfluoroalkyl tin (IV) halides with carbonyl compounds (Eqn. 8). The best yields of α-trifluoromethyl carbinols were obtained using $RfSnCl_2I$ rather than $RfSnF_2I$.

$$RfSnCl_2I \xrightarrow{Pyr.} [RfSnCl_2I(Pyr.)_n] \xrightarrow{RC(=O)R'} Rf-\underset{R'}{\overset{R}{C}}-OSnCl_2I(pyr.)_n \xrightarrow{H^+} Rf-\underset{R'}{\overset{R}{C}}-OH \qquad (8)$$

Some of the carbonyl compounds used as electrophiles in this reaction and the resulting yields are shown in Table II.

Table II

Carbonyl	RfI	Product	Yield (%)
PhCHO	CF_3I	$PhCH(OH)CF_3$	18
PhCHO	$i\text{-}C_3F_7I$	$PhCHO(OH)C_3F_7$	86
$n\text{-}C_4H_9CHO$	$n\text{-}C_3F_7I$	$n\text{-}C_4H_9CH(OH)C_3F_7$	68
	$n\text{-}C_3F_7I$		57
PhCOMe	$i\text{-}C_3F_7I$	$PhC(OH)(Me)C_3F_7$	37

Perfluoroalkyl radicals as reactive intermediates

Several methods for the generation of perfluoroalkyl free radicals and their reactions with organic substrates are known. CF_3I may be homolytically cleaved by ultraviolet light and adds across olefinic double bonds.[14] Trifluoromethyl radicals have been generated in a low temperature radio frequency discharge by homolytic cleavage of hexafluoroethane and used to substitute halogens in aromatic and aliphatic systems.[15] Trifluoromethyl radicals have also been generated by electrolytic decarboxylation of trifluoroacetic acid in $CH_3CN/H_2O/NaOH$ solutions and react to give addition products to olefins.[16]

A more versatile and selective method of radical perfluoroalkylation has been developed by Meijere.[17] He irradiated trifluoromethylazo compounds $\underset{\sim}{5}$ and the radicals generated recombine in their solvent cages giving good yields when solvents such as tert-butyl alcohol or hexadecane are used (Eqn. 9). The trifluoromethyl azo compounds are easily prepared by condensation of trifluoronitrosomethane with an amine. The amine may be bonded to a 1°, 2° or 3° carbon center.

$$R\text{-}NH_2 \xrightarrow[MeOH/-70°C]{CF_3NO} R\text{-}N{=}N\text{-}CF_3 \;(\underset{\sim}{5}) \xrightarrow[-N_2]{h\nu} R\text{-}CF_3 \qquad (9)$$

The intermediate azo compounds $\underset{\sim}{5}$ are stable at room temperature and are isolable by gas chromotography. Some of the products and their yields from this reaction are shown in Table III.

Table III

Amine	Yield of $\underset{\sim}{5}$ (%)	Yield of $R\text{-}CF_3$ (%)
n-Hexyl	80	42
Cyclohexyl	70	43 (18% )
Adamantyl	74	40

Copper(I) Coupling Reactions

Elemental copper reacts readily with perfluoroalkyl iodides in the presence of polar aprotic solvents such as DMF, DMSO, HMPA and pyridine to form solvated perfluoroalkyl complexes $\underset{\sim}{6}$ (Eqn. 10).[18a,19]

$$RfI \xrightarrow[Solvent(L)]{Cu} \underset{\sim}{6}\ RfCuL_3 + ICuL_3 \qquad (10)$$

Solutions of $\underset{\sim}{6}$ are sensitive to O_2 but resistant to hydrolysis. Room temperature solutions of $\underset{\sim}{6}$ are stable for months. The perfluoroalkyl copper complexes react with alkyl, olefinic and aromatic iodides or bromides to give the corresponding perfluoroalkyl compounds (Eqn. 11)

$$RfCuL_3 \xrightarrow{RX(X = Br,I)} R\cdots X\cdots Rf\cdots CuL_3 \longrightarrow R\text{-}Rf + XCuL_3 \qquad (11)$$

The mechanism of this reaction is not well understood but is believed to go through a cyclic transition state (Eqn. 11).[18a,b]

McLoughlin has published results of reactions of perfluoroalkyl copper complexes with a variety of aryl iodides.[18] Most substitutents on the aromatic ring are unaffected by this reaction. Some of the results are shown in Table IV.

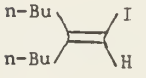
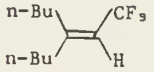
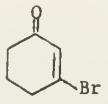
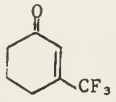
Table IV[a]

Iodofluoroalkane	Aryl Iodide	Solvent	Product	Yield (%)
C_3F_7I	C_6H_5I	DMSO	$C_3F_7C_6H_5$	65
C_3F_7I	m-$AcOC_6H_4I$	DMF	m-$C_3F_7H_4OAc$	65
$C_3F_{11}I$	p-$HO_2CC_6H_4I$	DMSO	p-$C_3F_{11}C_6H_4CO_2H$	65
$C_9F_{19}I$	m-$H_2NC_6H_4I$	DMSO	m-$C_9F_{19}C_6H_4NH_2$	45
$I(CF_2)_3I$	m-$MeOC_6H_4I$	DMF	$(m\text{-}MeOC_6H_4CF_2)_2CF_2$	55
$I(CF_2)_3I$	m-$O_2NC_6H_4I$	DMF	$(m\text{-}O_2NC_6H_4CF_2)_2CF_2$	52

a. The reactions were carried out under inert atmospheres of N_2 or Ar at temperatures of 110° - 130°C.

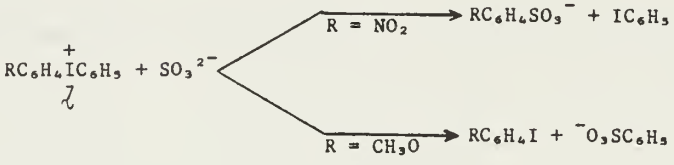
Kobayashi has studied the reactions of trifluoromethyl copper in HMPA with assorted alkyl and olefinic halides.[19] Some exemplary results are given in Table V.

Table V

Alkyl or Olefinic Halide	Product	Yield (%)
$PhCH_2Br$	$PhCH_2CF_3$	65
$n\text{-}C_{10}H_{21}I$	$n\text{-}C_{10}H_{21}CF_3$	48
	$n\text{-}C_{10}H_{21}F$	6
		62
		40

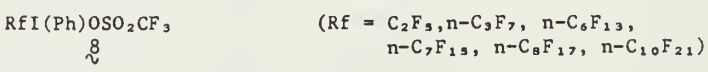
Electrophilic methods of perfluoroalkylation

Diaryliodonium salts 7 are known to undergo competitive arylation of nucleophiles, reacting at the more electron deficient aryl group.[20] Using sulfite ion as a nucleophile, Beringer found that a 4-nitrophenyl group was much more reactive and a 4-methoxyphenyl group was much less reactive than the unsubstituted phenyl group (Eqn. 12).



(12)

Using this information and related work by other authors,[21] Umemoto developed the electrophilic perfluoroalkylating agent 8.[22]



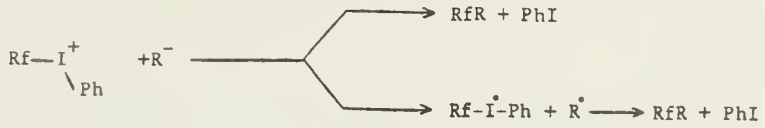
The perfluoroalkylphenyliodonium triflate 8 reacts with alkyl, allyl, benzyl and alkynyl carbanions to give the corresponding perfluoroalkyl compounds (Table VI).[23] In each case iodobenzene was recovered in nearly

Table VI[a]

Rf	R^-M^+	Product	Temp(°C)	Yield (%)
$n\text{-}C_8F_{17}$	$n\text{-}C_8H_{17}MgCl$	$n\text{-}C_8H_{17}C_8F_{17}$	-78	65
$n\text{-}C_3F_7$	$PhCH_2MgCl$	$n\text{-}C_3F_7CH_2Ph$	-110	82
$n\text{-}C_8F_{17}$	$CH_2{=}CHCH_2MgCl$	$n\text{-}C_8F_{17}CH_2CH{=}CH_2$	0	51
$n\text{-}C_3F_7$	$PhC{\equiv}CLi$	$n\text{-}C_3F_7C{\equiv}CPh$	-110	44

a. Reactions are run in THF

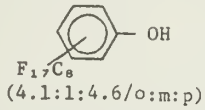
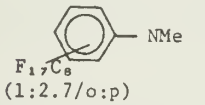
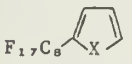
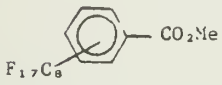
quantitative yield. The mechanism of these reactions is not well understood and may be direct nucleophilic attack of the carbanion or prior electron transfer from the carbananion to the iodine atom followed by reaction of Rf• with R• (Eqn. 13).



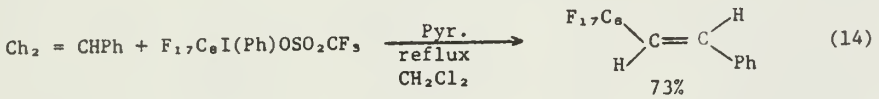
(13)

Umemoto has also studied the reactions of 8 with aromatic compounds.[24] He reports that π-electron rich aromatic compounds such as phenol, dimethyl aniline, furan, thiophene and pyrrole react readily at temperatures between 0°C and room temperature whereas π-electron deficient aromatic compounds (e.g. methyl benzoate) react only at elevated temperatures (Table VIII).

Table VIII

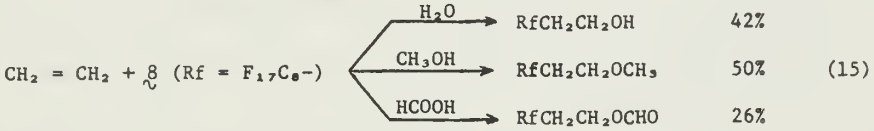
Product	Yield (%)	Base	Solvent	Temperature
 (4.1:1:4.6/o:m:p)	55	Pyridine	CH_2Cl_2	room
 (1:2.7/o:p)	37	--	CH_3CN	room
 X=O	87		CH_2Cl_2	room
X=S	73	Pyridine	CH_2Cl_2	room
X=NH	92		CH_2Cl_2	room
 (1:1:1.3/o:m:p)	54	Pyridine	CH_3CN	reflux

The perfluoroalkylphenyliodonium triflates 8 also react with olefins.[25] Umemoto found that styrene reacted with 8 to give trans-β-perfluoroalkyl styrenes (Eqn. 14).



(14)

Umemoto was also able to trap the intermediate carbonium ion formed by addition of Rf^+ to alkenes with various nucleophiles (Eqn. 15).



(15)

Summary

The number of perfluoroalkylation methods has increased rapidly in the last few years. Much work remains to be done to explore the limits of these reactions. The versatility and selectivity of these methods will undoubtedly open the way to new and previously inaccessible perfluoroalkyl substituted organic molecules.

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SELENOXIDES AND TELLUROXIDES AS MILD OXIDIZING AGENTS

Reported by Cynthia K. Loop February 17, 1983

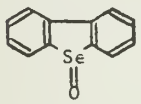
In recent years an increasing interest has developed in the chemistry of organoselenium and organotellurium compounds.[1] The need for mild oxidizing agents has resulted in investigations of many possible compounds. Because of the known properties of sulfoxides as oxidizing agents,[2] an interest in the oxidizing ability of selenoxides and telluroxides developed. Selenoxides and telluroxides should be more easily reduced than the corresponding sulfoxides due to the weaker oxygen bonds in the telluroxides and selenoxides.[3]

The preparations of selenoxides and telluroxides are usually accomplished by the oxidations of the corresponding selenide and telluride respectively or by the hydrolysis of the corresponding selenide dihalide and telluride dihalide respectively.[4]

Selenoxides have been used to oxidize sulfides to sulfoxides.[1e,4,5] This has been accomplished at room temperature with an acid catalyst or by exposing the reaction to ultraviolet light. No sulfones were observed in either case, T. Tezuka, H. Suzuki, and H. Migazaki studied the photochemical reaction. Their results are shown in Table I. There was no observed reaction when diphenylsulfide was present with either of the two selenoxides listed in Table I. Methylphenylsulfide was not observably oxidized thermally below 80°C using the same reaction solutions as for the photoreactions. Diphenylselenoxide did not photooxidize cyclohexene or stylene. Molecular oxygen was not trapped when 9,10-diphenylanthracene was present in the reaction solution. The reaction was not quenched by β-carotene. Therefore, it is possible that atomic oxygen is liberated photo-

Table I.

Results from Photochemical Reactions.

Selenoxide	Eq. used	sulfide (1eq)	solvent	product (yield, %)
Ph_2SeO	2	MeSPh	CH_2Cl_2	MeS(O)Ph (40)
	3	n-Bu_2S	MeOH	n-Bu_2SO (97)
	3	n-Bu_2S	CH_2Cl_2	n-Bu_2SO (77)
	3	$(CH_2)_5S$	MeOH	$(CH_2)_5SO$ (78)
	3	$(CH_2)_5S$	CH_2Cl_2	$(CH_2)_5SO$ (60)
	3	MeSPh	MeOH	MeS(O)Ph (87)
	3	MeSPh	CH_2Cl_2	MeS(O)Ph (64)

chemically from the selenoxide which reacts with the sulfide or an excited molecule of selenoxide reacts with the sulfide to form a bimolecular species which collapses to the products. However, since olefins were not oxidized this would indicate that atomic oxygen is not involved.

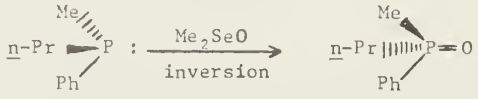
Dimethylselenoxide has been used as an oxidizing agent in various reactions at room temperature,[6] whereas reactions using dimethylsulfoxide usually

require elevated temperatures or a catalyst.[2] Trivalent phosphorus compounds have been oxidized to the corresponding phosphine oxides.[6]

$$R_3P: + Me_2SeO \xrightarrow[R.T.]{} R_3P{=}O + Me_2Se$$

R = Ph, EtO, Et_2N

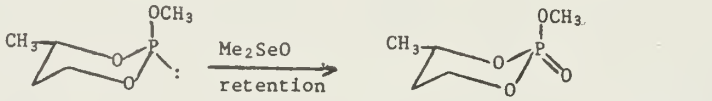
The reaction is quantitative after approximately one hour as shown by TLC. The reaction proceeds with inversion if the phosphine is acyclic.



(S)-methyl-n-propylphenylphosphine ⟶ (S)-methyl-n-propylphenylphosphine oxide

$[\alpha]_{589}$ + 15.21°(78%op) $[\alpha]_{589}$ - 14.80°(74%op)

However if the compound is cyclic, the reaction proceeds with retention.

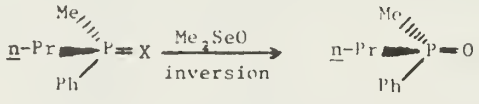


85% yield

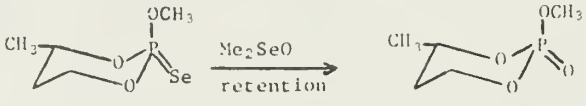
trans-2-methoxy-4-methyl-1,3,2-dioxaphosphorinane (100%dp) — trans-phosphate (100%dp)

Mechanisms involving nucleophilic attack of phosphorus on the selenium atom have been proposed but little research has been done to support them.

Thiophosphoryl compounds and selenophosphoryl compounds have been converted to phosphine oxides by dimethylselenoxide. Again there is inversion when the phosphorus compound is acyclic and retention when the phosphorus compound is cyclic.



X = S,Se



83% yield

cis-2-methoxy-2-seleno-4-methyl-1,3,2-dioxaphosphorinane (100%dp) ⟶ trans-phosphate (100%dp)

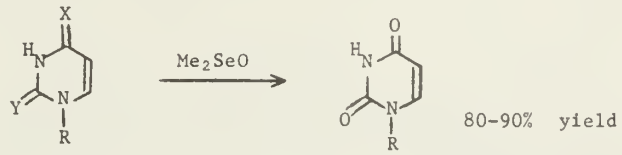
Acyclic ureas are produced from thioureas at room temperature.

$$(RNH)_2C{=}S + Me_2SeO \longrightarrow (RNH)_2C{=}O + Me_2Se + S_8$$

R = H, i-Pr, t-Bu, cyclohexane

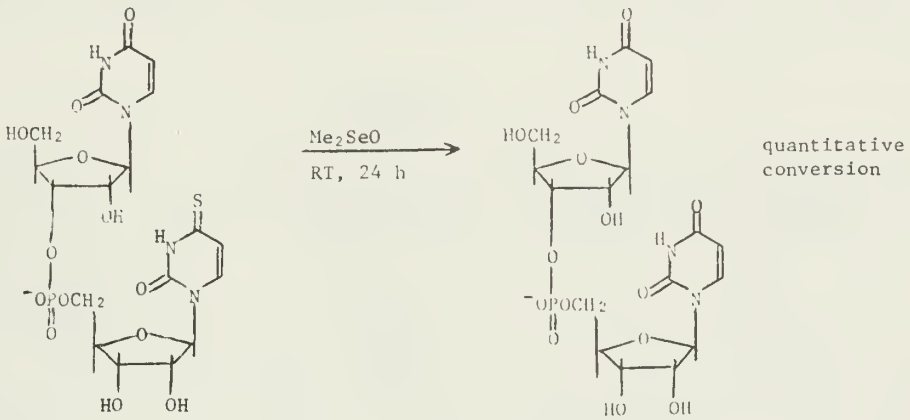
R + R = $-CH_2CH_2-$

Cyclic ureas are obtained at 40°C after about 6 hours in good yield.

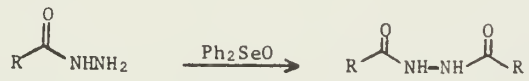


Y = O,S X = S,O R = H, ribofuranosyl

In the reaction of uridylyl-(3'-5')-4-thiouridine with dimethylselenoxide, the internucleotide bond is stable under the reaction conditions. Also, no degradation of the sugar moiety was observed.

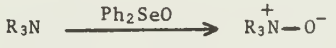


Diphenylselenoxide has been utilized to form symmetric diacyl hydrazines from acyl hydrazines.[5a]



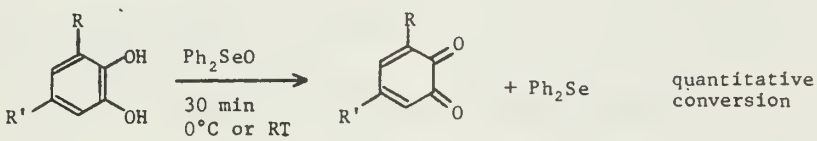
R = Ph, m-$NO_2C_6H_4$, PhNH, $HO_2CCHNH_2CH_2$

Tetiary amines are converted to N-oxides.

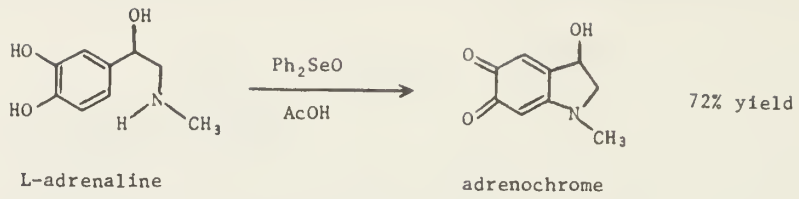


R_3N = Me_3N, Et_3N, brucine, strychnine, nicotinamide

Catechols and hydroquinones are oxidized by diphenylselenoxide whereas simple phenols are unaffected under reaction conditions.[7]



R = R' = t-Bu R = H; R' = t-Bu

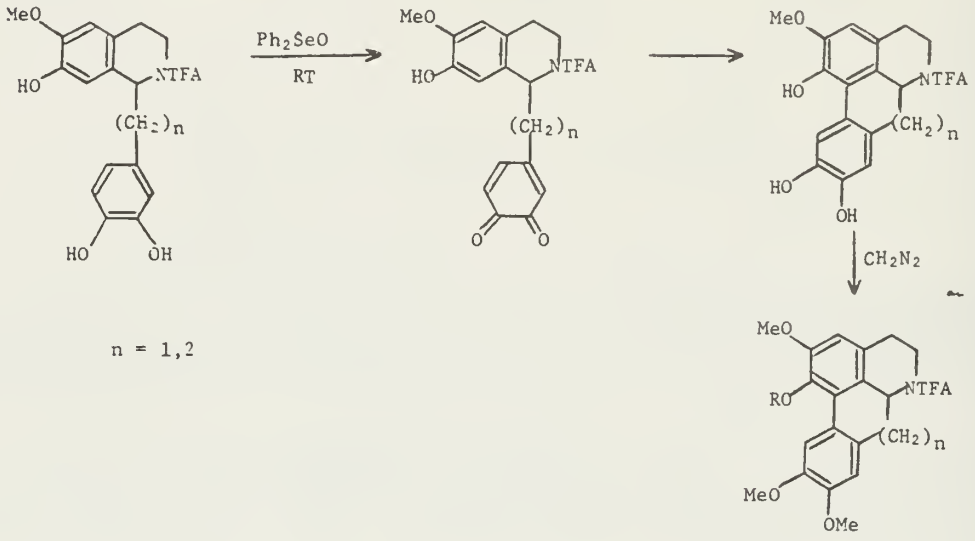


L-adrenaline adrenochrome 72% yield

Adrenochrome produced by this method is stable at room temperature for several months.[8]

An application of diphenylselenoxide used as an oxidizing agent is shown in Scheme I. When o-chloranil was used as the oxidant, less than 10% yield of 1 was obtained.

Scheme I.

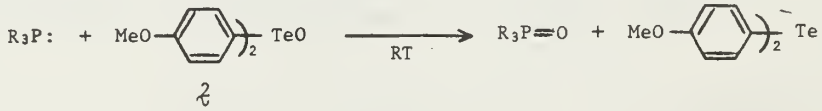


n = 1,2

1 R = H n = 1 80% yield
R = Me n = 2 55% yield

Another area of research involves using selenoxides on a polymer support.[9] This would facilitate the separation of the product from the reactants since the oxidizing agent is bound to an insoluble polymer support. In addition the toxicity of the oxidizing agent could be significantly reduced. The reuse of the polymer reagent is possible in the same manner as the unbound selenides by oxidizing the resulting selenides back to the selenoxide.

More recently telluroxides have been studied as oxidants.[3] Bis(p-methoxyphenyl)telluroxide, 2, oxidizes phosphines to phosphine oxides.



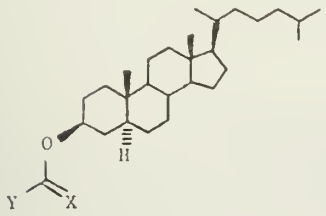
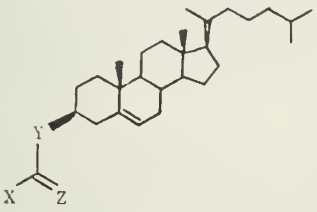
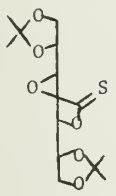
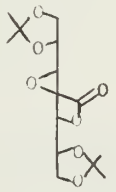
2

R = n-Bu 97% yield 71% yield
R = Ph 80% yield 73% yield

Thiocarbonyl compounds and selenocarbonyl compounds are converted to carbonyl compounds in the presence of 2, Table II. In only one case, trithiocarbonate, the product was inseparable from the reaction mixture.

Table II.

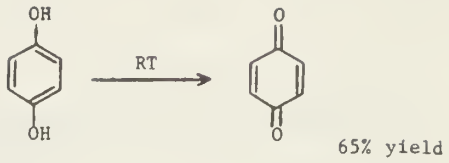
Results Using 2 as Oxidant.

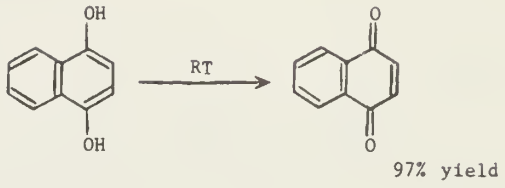
Compound		reaction time (h)	product	yield, %
	X = S Y = SMe	24	X = O Y = SMe	Quant
	X = Se Y = Ph	0.3	X = O Y = Ph	93
	X = Ph Y = O Z = S	1.5	X = Ph Y = Z = O	66
	X = Me Y = O Z = S	0.25	X = Me Y = Z = O	Quant
	X = Ph Y = S Z = S	27	X = Ph Y = S Z = O	70
$(RNH)_2C=S$	R = H	16	$(RNH)_2C=O$	Quant
	R = Ph	16		68
		0.5		96
$CH_3(CH_2)_{17}O-C(=S)-Ph$		4	$CH_3(CH_2)_{17}O-C(=O)-Ph$	91
t-Bu_2CS		0.3	t-Bu_2CO	Quant
		20		87
		42		23

[a]Quant = Quantitative conversion

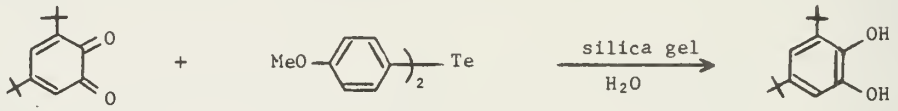
Thiols are oxidized to disulfides. Thiobenzyl alcohol and p-thiocresol are oxidized to give the corresponding disulfides in greater than 95% yield.

Catechols and hydroquinones are oxidized in the presence of 2. When 3,5-t-butylcatechol was oxidized, the ^1H NMR showed only the telluride and the quinone present. However, no telluride was obtained from the separation by column





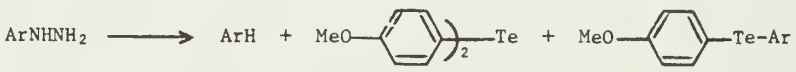
chromatography and catechol as well as the quinone were obtained. A mixture of the telluride and quinone was made from authentic material. The ^{1}H NMR showed only the telluride and quinone. Quinone, catechol, and a trace of the telluride were obtained by TLC from this mixture. Therefore, the reverse reaction is taking place on the silica gel.



Symmetric diacyl hydrazines are formed from acyl hydrazines in the presence of 2.



When aryl hydrazines were treated with 2, the parent arene as well as symmetrical and unsymmetrical diaryl tellurides are obtained.



Ar = Ph, 4-MeC$_6$H$_4$, 2,6-(diMe)C$_6$H$_3$, 4-BrC$_6$H$_4$, 4-HO$_2$CC$_6$H$_4$

Dithiolanes, enamines, aldehydes, ketones, alcohols, pyrroles, indoles, amino acids, aromatic amines, monohydroxylated aromatics, esters, hindered thiocarbamates, isonitriles, oximes, aryl hydrazones, sulfides, and selenides are unaffected by 2.

Some kinetic work shows that 2 reacts about twice as fast with 3,5-t-butylcatechol than with the xanthate, 3. However, p-thiocresol is selectively oxidized in the presence of 3,5-t-butylcatechol.

An application of telluroxide in a catalytic oxidative process has been investigated based on Scheme II. Potassium carbonate was the best base found but triethylamine could be used. The use of 1,2-dibromotetrachloroethane as the halogenating agent resulted in 80% yield of the diaryltellurium dibromide at room temperature. Table III shows the results with some thiocarbonyl compounds.

Scheme II.

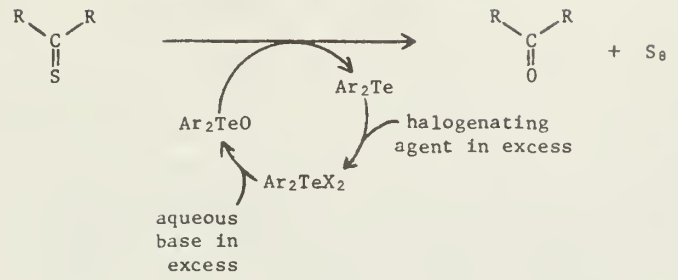
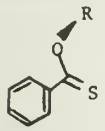
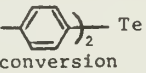


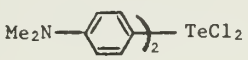
Table III.

Some Results with Thiocarbonyl Compounds.

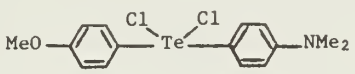
Compound	Eq. Halogenating Agent	Eq. Te species[a]	Aq. base	Time (h)	yield, %
	1.1	0.1	10% K_2CO_3	116	88
	3	0.1	10% K_2CO_3	23	90
	5	0.015	10% K_2CO_3	88	75
	5	0.015	20% K_2CO_3	20	70
	3	0.015	20% K_2CO_3	80	70
	5	1	Et_3N	15	85
R = cholesteryl	5	0.1	Et_3N	48	41
t-Bu_2CS	5	0.015	20% K_2CO_3	15	Quant[b]

[a]The Te species is 

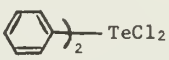
[b]Quant = Quantitative conversion



4



5



6

The rates of a few diaryltellurium dichlorides were compared for the hydrolysis to the diarytelluroxide with potassium carbonate as the base in the order 4>5>>6.

The major objections to using organoselenium or organotellurium compounds are their odor, toxicity, and cost. The cost can be countered in this case since the organoselenides and organotellurides are usually recovered in greater than 70% yield.[3,6] and can be reoxidized to the organoselenoxides and organotelluroxides. Selenoxides are generally colorless and odorless.[10] The telluroxide, 1, is also odorless and soluble in most organic solvents. Odors often indicate the presence of impurities. In addition, in some cases these reagents may be preferable. For example, the adrenochrome synthesized from L-adrenaline is more stable if diphenylselenoxide is used instead of silver oxide. Another example was given in Scheme I. If o-chloranil is used as the oxidizing agent, the yield decreases from 80% to less than 10%. However, there still remains a large amount of research to be done especially on the mechanisms of the reactions and their selectivity.

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PREPARATION OF HYDANTOIN CHIRAL STATIONARY PHASES AND RESOLUTION OF ENANTIOMERS

Reported by Myung Ho Hyun February 21, 1983

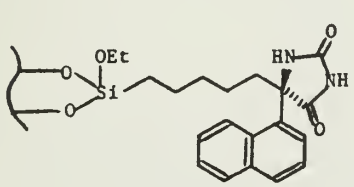
The ascertainment of enantiomeric purities, the determination of absolute configuration and the procurement of enantiomerically pure materials have been commonly encountered stereochemical problems. An almost ideal means for simultaneous solution of all three of these problems would be the direct chromatographic separation of enantiomers upon a chiral stationary phase.

Since the importance of the "three point rule" was first recognized for the chromatographic resolution of enantiomers,[1] many advances have been made in the direct resolution of enantiomers upon chiral stationary phases.[2] Prominent examples include the resolution of chiral helicenes,[3] the resolution of amino acid and ester salts upon a chiral crown ether based stationary phase[4] and the optical resolution using chiral polymeric packing material.[5]

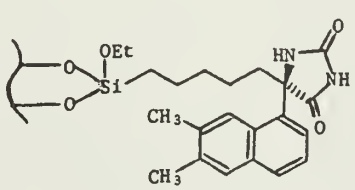
While no chiral stationary phase will ever separate all enantiomers, Pirkle and coworkers have reported the preparation of a fluoroalcohol chiral stationary phase which is capable of resolving a relatively broad spectrum of racemates.[6] In 1981, the ionically bonded N-(3,5-dinitrobenzoyl)phenylglycine chiral stationary phase, which shows even greater generality than does the fluoroalcohol chiral stationary phase, was also reported.[7] Racemic aryl-substituted hydantoins are readily resolvable on the ionically bonded N-(3,5-dinitrobenzoyl)phenylglycine chiral stationary phase.[7b,c] From the point of view of reciprocality in chiral recognition,[7a] a hydantoin readily resolvable upon the N-(3,5-dinitrobenzoyl)phenylglycine chiral stationary phase should, after resolution, be capable of affording a chiral stationary phase that will separate racemic amino acid derivatives.

Starting from 1-naphthoic acid, the hydantoin chiral stationary phase $\underset{\sim}{1}$ has been prepared. Hundreds of 3,5-dinitrobenzamides derived from amines, amino acids, aminoalcohols and aminoesters have been resolved on the hydantoin chiral stationary phase $\underset{\sim}{1}$. Chiral recognition models involving multiple simultaneous stereochemically dependent interactions are advanced to account for the elution orders of racemates and for the magnitude of the enantiomeric separability factors. On the basis of the chiral recognition model, rational improvements in the design of a hydantoin chiral stationary phase may be made. For example, enhancing the π-basicity of the naphthyl system should increase the degree of chiral recognition. Starting from 2,3-dimethylnaphthalene, the second hydantoin chiral stationary phase $\underset{\sim}{2}$ has been prepared and has shown a marked improvement over chiral stationary phase $\underset{\sim}{1}$.

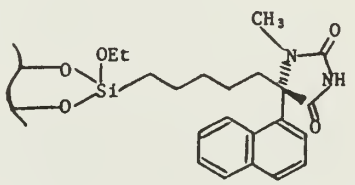
Chiral stationary phase $\underset{\sim}{3}$ has also been prepared and evaluated relative to chiral stationary phase $\underset{\sim}{1}$.



$\underset{\sim}{1}$



$\underset{\sim}{2}$



$\underset{\sim}{3}$

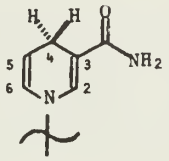
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METAL ION-CATALYZED NADH MODEL REACTIONS

Reported by Stephanie J. Brandes February 24, 1983

Certain enzymes which catalyze the reduction of compounds such as ketones, aldehydes, and α,β-unsaturated ketones, require the reduced form of nicotinamide adenine dinucleotide (NADH) as a coenzyme. In addition, a divalent metal ion appears necessary for catalysis to occur. Many attempts have been made to elucidate the intermediates and reaction path of these enzyme-NADH-metal ion systems and to determine the role the metal ion plays. The work has centered around the use of salts of certain metals, such as zinc and magnesium, and NADH derivatives containing the active unit of the coenzyme, the dihydronicotinamide moiety (1). The results of these studies will presently be discussed.

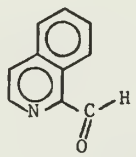


1

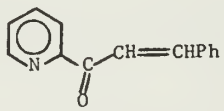
Reactant Activation.

Many model reactions with no metal present yield little, if any, reduced product.[1] Therefore, probably one of the most important roles of the metal ion is to activate the substrate, the nicotinamide derivative, or both. Which reactant is activated, however, and the manner in which activation occurs is still under inquiry.

Several workers propose substrate complexation. A catalytic model has been postulated which includes an electrophilic catalyst in close proximity, as a result of its coordination to a suitable site on the protein matrix, to the moiety to be activated.[2] The model may be illustrated by employing a substrate with two possible sites of chelation, one of which could act to position the metal ion near the other. The latter site is often the oxygen of a carbonyl or aldehyde. Sample compounds include 2-benzoylpyridine (2-BP), 2-acetylpyridine (2-AP), pyridine-2-carboxaldehyde (2-PCA), isoquinoline-1-carboxaldehyde (2), and 2-cinnamoylpyridine (2-CP) (3). In some cases, bidentate chela-



2



3

tion has been found to occur.[1d,e,g,2] Proof of this is seen in significant rate enhancements of the above molecules as compared to the isomers where the two complexing sites are remote from each other, e.g. 3- or 4-CP (Table I). Da-

Table I.

Bimolecular rate constants for reduction of 2-, 3-, 4-cinnamoylpyridine by N-benzyl-1,4-dihydronicotinamide (CD_3CN, 23°C; Substrate = Reductant = $Mg(ClO_4)_2$ = 0.4M).[2]

Substrate	k_2 M^{-1} min^{-1}	rel rate
2-CP	10.3	1590
3-CP	6.5×10^{-3}	1
4-CP	3.2×10^{-2}	5

ta from other studies concurs.[1d,e] Although the reduction of 3- or 4-CP is significantly slower, their reaction is more facile than if there were no metal present.[2] A mixture of 3- or 4-CP and N-benzyl-1,4-dihydronicotinamide (NBDN) in CD_3CN at room temperature shows no change in the ^1H NMR over a period of three days except for a slow decrease in intensity of the NBDN signal.[2] It has been suggested by Pandit, Gase,[2] and others[1d,e] that this acceleration is due to the metal ion exerting electronic effects through the substrate's aromatic ring. Other groups, though, have found that such compounds do not react in the presence of metal and a reducing agent.[3]

Reduction of substrates whose structures permit only monodentate chelation is also enhanced when metal ion is present.[4] In particular, Ohnishi et al.[4b] determined the yield of phenyl trifluoromethyl carbinol to be 3% in the reduction of trifluoroacetophenone with NBDN. The reaction was run for a day at 30°C. Upon inclusion of magnesium perchlorate, the yield under the same conditions increased to 20%.

An activated metal-substrate complex is questioned by some researchers.[3c,4] Upon addition of $ZnBr_2$, $Zn(ClO_4)_2 \cdot 6H_2O$ or $Zn(CH_3COO)_2 \cdot 6H_2O$, Hughes and Prince noted no perturbation in the UV spectrum of 2-PCA in acetonitrile.[3c] They therefore infer that there is only weak interaction between metal and substrate. Large downfield shifts ($\Delta\delta$ on the order of 30-35 Hz) of certain protons in the proton NMR of 2-PCA in the presence of $ZnBr_2$ show that there is some interaction.[6] They further believe that inhibition in the reaction of 2-PCA with NBDN arises as a result of an unreactive $(ZnX^+ \cdot 2\text{-PCA})$(X is a counter ion) complex which does finally form. (For a full explanation, see the results of Hughes and Prince[3c] under activating metal-reductant complexes.) Ohno proposes that since the reaction rate for reduction of methyl benzoylformate by an NADH model is independent of the concentration of $Mg(ClO_4)_2$, the possibility of the initial formation of a complex between substrate and magnesium is precluded (Table II).

Table II.

Dependence of reduction rate on the concentration of magnesium perchlorate. (CH_3CN, 25°C). S = Benzoylformate; R = N-α-methylbenzyl-1-propyl-1,4-dihydronicotinamide.[5a]

[R] x 10^4, M	[$Mg(ClO_4)_2$] x 10^3, M	[S] x 10^3, M	k_{obsd} x 10^2, min^{-1}	k_{calcd}, M^{-1} min^{-1}
2.00	3.91	11.92	8.16 ± 0.30	6.84 ± 0.31
2.00	6.06	11.74	7.86 ± 0.30	6.70 ± 0.30
1.99	6.03	12.21	8.26 ± 0.31	6.76 ± 0.30
2.00	11.91	11.92	8.53 ± 0.31	7.15 ± 0.31
2.00	23.81	12.34	8.36 ± 0.31	6.77 ± 0.30
2.00	35.70	12.40	8.00 ± 0.30	6.45 ± 0.30

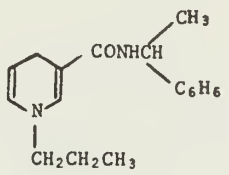
Activating metal-reducing agent complexes have been suggested also.[1a,b, 3a,5a,6,7] These types of complexes have been postulated as a result of NMR, UV, and IR studies. Some question remains as to the manner in which the metal associates with the coenzyme model.[3a,6,7] Pandit et al.[3a] found that H-2 of NBDN shows the greatest variation in shift in proton NMR when metal is present. In ^{13}C NMR, C-2 and the carbonyl carbon are shifted downfield and C-3 is shifted upfield. Hughes and Prince noted changes in the carbonyl region of the IR spectrum upon addition of $ZnBr_2$ to NBDN in acetonitrile (Table III). These

Table III.

NBDN IR absorption bands which are altered upon metal salt addition. (CD_3CN)[6]

	Wavenumber(cm^{-1})				
NBDN	3502m	3387m	1692vs	1654s	1581vs
($ZnBr_2$·NBDN)	3440(w,b)	3330(w,b)	1684vs	1644s	1608m

workers thus feel that the metal could be coordinated at the amide oxygen. However, Ohno et al.[7] noted no difference in the IR spectrum of N-(α-methylbenzyl)-1-propyl-1,4-dihydronicotinamide (4) with and without $Mg(ClO_4)_2$. Paul et al.[8] synthesized ($ZnCl_2$· nicotinamide) and detected little or no change in



4

the IR absorption bands due to the amide C = O, C - N, and N - H moieties as compared to these bands in the spectrum of free nicotinamide. This, and the fact that a shift in the UV maximum is observed when metal is included in an acetonitrile solution of 4 suggests that chelation does occur, but at another possible complexation site in the molecule, the nitrogen of the pyridine ring.[7]

In the reduction of methyl benzoylformate, formation of a complex between magnesium ion and reducing agent appears important.[7] The absorption maximum in the UV spectrum of reducing agent shifts towards longer wavelengths upon addition of increasing amounts of $Mg(ClO_4)_2$. The spectra are not affected by the presence of substrate. Kinetic studies performed by Hughes and Prince[3c] specify a half-order dependence of reaction rate on metal salt concentration. From this, they feel that the actual metal species binding to the coenzyme model is MX^+, where X is a counter ion.[3c] The authors postulate that the maximum rate occurs when the concentration of metal salt is sufficient to completely chelate the NBDN present. The reducing agent will be complexed in preference to 2-PCA. It appears that the NBDN associates more readily with the metal than does 2-PCA. $Zn(ClO_4)_2 \cdot 6H_2O$ and $ZnBr_2$ shift the NBDN UV maximum from 346 nm, which is the absorbance for free NBDN, to higher wavelengths. However, as noted above, UV indicates only weak interaction between the metal and 2-PCA. At concentrations greater than that required to chelate the NBDN, (MX^+ · 2-PCA) complex will accumulate. Since all NBDN is bound at this point, a reactive intermediate with the substrate and reductant in close proximity to each other will not be able to form and the reaction rate will decrease.[3c] In a typical experiment

with [NBDN]= 10^{-4}M and [2-PCA]= 10^{-2}M, the maximum rate (k_{obs} = $2x10^{3}$ sec^{-1}) was reached at [$Zn(ClO_4)_2$]= $8x10^{-3}$M, and declined to k_{obs} = $9x10^{2}$ sec^{-1} at [$Zn(ClO_4)_2$]= $4x10^{-2}$M.

Evidence has been presented that can be interpreted against an activating coenzyme model-metal complex.[9] The reduction of hexachloroacetone[9b] is decelerated by the inclusion of metal ion. Formation of a metal- NBDN complex, as shown by UV, hinders the reaction.[9b]

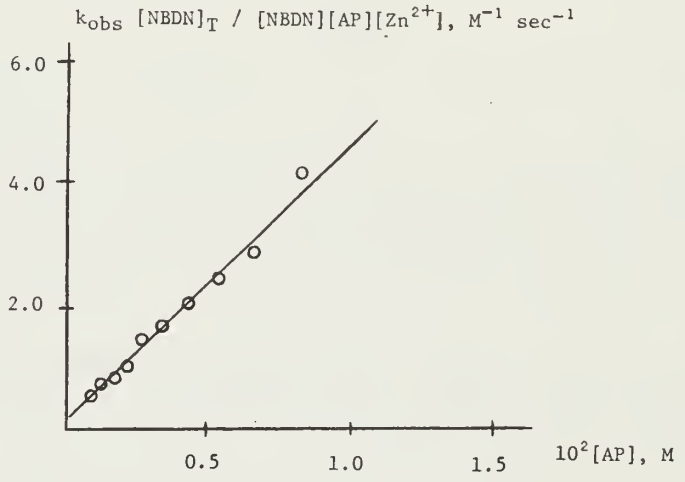
Gase, Ohno et al. conclude that NBDN-metal ion complexes, as well as substrate-metal complexes, are reacting species in the zinc-catalyzed reductions of 2-AP and 2-BP.[10] If the following reactions are assumed:

$$\left.\begin{array}{rl} BM + S & \xrightarrow{k_1} \\ B_2M^{11} + S & \xrightarrow{k_2} \\ SM + B & \xrightarrow{k_3} \\ S_2M^{12} + B & \xrightarrow{k_4} \end{array}\right\} \text{products}$$

where B is NBDN, S is substrate - 2-BP or 2-AP, and M is zinc ion, a rate expression may be derived which requires that a straight line be obtained when k_{obs} $[B]_T$ / [B][S][M] is plotted against [S]. Such a line is procured when experimental data are graphed.

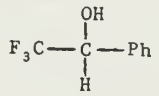
Figure 1.

Dependence of the observed rate on the concentration of 2-acetylpyridine in acetonitrile at 50°C.



Mechanism.

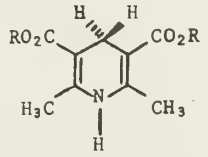
While it is not known with certainty what type of reactant complexes are initially formed, many agree that a transition state consisting of a ternary complex including both reagents and a metal ion is plausible.[1g,3a,c,6,7,13] Probably the strongest evidence to suggest the formation of this complex is found in the stereospecificity of NADH model reactions.[1b,4b,13] Trifluoroacetophenone is reduced by optically active 4 in the presence of Mg^{2+} to give either (R)- or (S)-phenyl trifluoromethyl carbinol (5).[4b] In particular, sub-



5

strate with (R)-4 and Mg^{2+} gave (S)-5 in 58% yield and 16% optical purity. This same reaction in the absence of magnesium gave racemic product in 30% yield.[4b] Binding of substrate and reductant to the metal in the transition

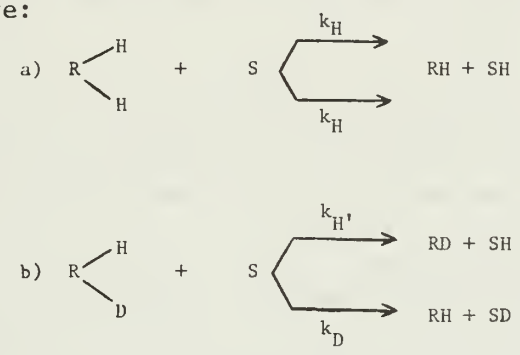
state is apparently so tight and specific that the chirality in the coenzyme model is easily transferred to the products.[4b,13] Nishiyama et al. noted that Hantzsch ester 6 asymmetrically reduced methyl pyruvate and benzoylformate to lactate and mandelate in optical yields of up to 21%.[13]



R = (-)-menthyl

6

Originally it was believed that the actual hydrogen migration involves movement of a hydride in a simple bimolecular reaction.[14] Data which imply that reduction is not bimolecular may be found in the widely documented divergence of the kinetic deuterium isotope effect, k_H / k_D, from the ratio of the amounts of isotopes incorporated in the product using a reducing agent monodeuterated at C-4 (isotope partitioning ratio, y_H / y_D).[1d,5b,6,15] Systems which have been tested usually exhibit a primary isotope effect from one to two; the partitioning ratio is closer to four or five (Table IV). Relevant reactions[16] are:



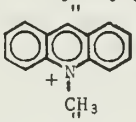
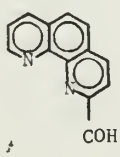
(1)

$$k_{1a} = 2k_H$$

$$k_{1b} = k_{H'} + k_D$$

Table IV.

Isotope Effects for Reductions by Monodeuterodihydronicotinamides.

Dihydronicotinamide	Substrate	Kinetic Deuterium Isotope Effect[a] $\left(k_{1a}/k_{1b}\right)$	Partitioning Ratio[b] y_H/y_D	Secondary Isotope Effect[c] $k_H/k_{H'}$	Reference
N-Propyl	$CF_3COC_6H_6$	1.38	3.8	0.87	15a
N-Benxyl	"	1.47	3.8	0.93	"
N-Propyl		1.26	5.4	0.75	15d
N-Benzyl		1.16	4.0	0.73	15b
N-2'-Carboxybenzyl	"	1.11	3.8	0.70	15c
N-Propyl		1.74	---	----	1d

[a] These observed values are affected by small secondary isotope effects which are present.
[b] Obtained from mass spec or NMR.
[c] Calculated values.

R is reducing agent and S is substrate. k_H is the rate of hydrogen transfer from C-4 of the reducing agent bound to two hydrogen atoms, k_H', the rate of hydrogen transfer from C-4 which is bound to a hydrogen and a deuterium, and k_D, the rate of deuterium transfer from C-4 bound to both a hydrogen and deuterium. Steffens and Chipman argue in the following manner against a one-step mechanism:[15a]

$$\left(\frac{k_{1a}}{k_{1b}}\right) = \frac{2k_H}{k_H' + k_D} \qquad (2)$$

For a reaction that is strictly bimolecular, y_H / y_D equals k_H' / k_D. If (2) is rearranged

$$\left(\frac{k_{1a}}{k_{1b}}\right) = 2\left(k_H / k_{H'}\right) \Big/ \left(1 + y_H / y_D\right) \qquad (3)$$

The term k_H / k_H' represents the secondary isotope effect. Values of the secondary isotope effect are included in Table IV. The data have been calculated using these formulas derived for a bimolecular mechanism. However, there has been no previous report of a secondary isotope effect of less than one for a system, like those above, in which a carbon atom is undergoing conversion from sp^3 to sp^2 hybridization. A bimolecular mechanism is not consistent with the observed isotope effects. Instead, it is proposed that at least one non-covalent intermediate, possibly a charge-transfer complex,[15a,b,d,17] is involved in the reaction. Sigman et al. think that they have observed such a complex and measured its absorption spectrum and rate of decomposition using flow spectrophotometry.[15b]

Although the isotope effects data do not override the possibility of hydrogen nucleus transfer occuring via a hydride, another mechanism has been suggested.[5a,b,7,10,15,18] This pathway assumes reduction proceeds while the reactants are situated in the ternary complex. An electron is transferred from the reducing agent, which causes the formation of a radical cation-radical anion pair. This is followed by migration of a proton and then movement of another electron. It is also possible that an electron and subsequent hydrogen atom are transferred.[5b,18c] Addition of NBDN to p,p'-dichlorobenzil (PDCB) in the presence of light gives a weak ESR spectrum identical with that of the radical anion of PDCB obtained in the t-BuOH-DMSO system.[18b] When this mixture contains $Mg(ClO_4)_2$, another ESR spectrum which is postulated to be the anion radical of PDCB associated with magnesium ion is recorded. The former ESR spectrum is converted to the latter by inclusion of Mg^{2+}[18b]. A cation-anion radical pair has been identified by ESR in the reduction of thiobenzophenone with NBDN.[18c]

If the reduction does follow such a three-step pathway, a metal ion could play an important part in the stabilization of the ternary transition state and promotion of the reduction therein. It is possible that it acts as an electron conductor. Shporer et al.[19] have reported that certain alkali and alkaline earth cations accelerate the rate of electron transfer between ferricyanide ($Fe(CN)_6^{4-}$) and ferrocyanide ($Fe(CN)_6^{3-}$) ions. For example, a 30-40-fold rate increase occurs in comparing H^+ to Rb^+. The authors consider a mechanism in which the electron is actually transferred by the cation from one anion to the other; the cation acts as a bridge. As a chelating agent, the metal ion could also contribute to stabilize[20] the anion radical by neutrali-

zing negative charge.[1d,9,21] Indirect proof that a metal ion can associate with a negatively charged species is found in Toeniskoetter and Solomon's work.[21a] This group has synthesized Co(II) complexes, CoL_2, with L as the enolate of 2,3-butanedione, 2,3-pentanedione and 1,2-cyclohexanedione. Since the magnetic and spectral properties of the complexes in solution indicate an octahedral coordination, it is postulated that two solvent molecules complex with the CoL_2 molecules so this geometry is obtained. A chelating structure is assumed. Ryan and Evans, studies[20b] on the effect of metal ions on the electrochemical reduction of benzil in non-aqueous solvents have enabled them to determine ion pair formation constants for K^+, Na^+, Li^+ and the benzil radical anion. In the reduction of benzil with barium, strontium or calcium perchlorate present, the shape of the cyclic voltammograms recorded and their dependence on scan rate were rationalized by a mechnaism including reversible reduction to the radical anion and rapid ion pair formation.

It has been suggested that the three-step electron-proton-electron mechanism is not a viable explanation for NADH model reactions.[22] Prince et al.[22a] used the spin trapping agent 2-methyl-2-nitrosopropane in the reduction of 2-PCA by NBDN and Zn^{2+}. Although an ESR spectrum was obtained when the reaction was illuminated, identical spectra under the same conditions were obtained for 2,6-lutidine, triethylamine and triphenylphosphine.[22a]

Conclusion.

Because of NADH model reactions, the ignorance surrounding certain aspects of the important class of pyridine nucleotide-dependent dehydrogenases has been dispelled to a certain extent. However much work remains to be done. It is believed that metal-reactant complexes and a mechanism involving at least one intermediate, whether it be a charge-transfer complex or species not yet determined, will play an important role in future studies of these systems.

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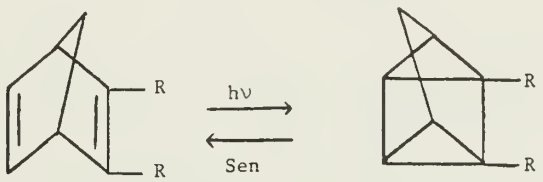
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MECHANISTIC STUDIES OF NORBORNADIENE/QUADRICYCLENE PHOTOSENSITIZED ISOMERIZATIONS

Reported by Stephen Lapin February 28, 1983

Introduction

The direct photochemical conversion of norbornadiene (1) to its valence isomer quadricyclene (2), has been known for some time.[1] Interest has recently been renewed in systems of this type due to the possibilities for reversible solar energy storage.[2] This review will examine mechanistic studies of the photosensitized isomerization of (1) ⟶ (2) and the reverse ring opening reaction (2) ⟶ (1). The review will also consider the methoxycarbonyl analogs of norbornadiene and quadricyclene (3) and (4).



1 R = H 2

3 R = $\overset{O}{\overset{\|}{C}}-OCH_3$ 4

It is well known that triplet photosensitizers such as benzophenone or acetophenone can be used efficiently in the conversion of (1) to (2).[3] Since (1) does not have a classically conjugated structure, one might expect that it would not be a good acceptor of electronic energy from sensitizers. It has been shown, however, that due to interaction between the two double bonds, the lowest electronically excited states are below those of simple olefins. The first absorption maximum is found at 222 nm. A transition at 4.0 eV has also been found using electron-scattering spectrometry. This excited state is believed to be the lowest triplet.[4]

The observation that some triplet sensitizers could also effect the reverse transformation, (2) ⟶ (1), was surprising to the initial investigators.[5] Since (2) is a saturated hydrocarbon, it seemed unlikely that it would have a low lying electronically excited state. When (1) or (2) is irradiated in the presence of acetophenone (E_T=73.6 kcal mol^{-1}) only (2) is present after photolysis. When either (1) or (2) is photolyzed in the presence of fluorenone (E_T=54 kcal mol^{-1}), photostationary states containing more than 70% of (1) are reached. It was postulated that (2) is undergoing excitation to a triplet with approximately the same nuclear configuration as would be formed by the excitation of (1). Since (2) is a higher energy isomer of (1), the (2) ⟶ (1*) process would be favored by sensitizers of lower triplet energy.[5]

Fluorescence Quenching

In 1968 Murov and Hammond[4] were studying the quenching of aromatic fluorescence by conjugated dienes. They unexpectedly discovered that (2) was a much more effective quencher than (1). By using Stern-Volmer kinetic relationships they found that k_q for the quenching of naphthalene fluorescence by (2) was 3.2×10^9 $M^{-1}s^{-1}$ while the k_q for (1) was 1.3×10^7 $M^{-1}s^{-1}$. They also showed that each quench by (2) resulted in isomerization to (1). Quenching of fluorescence by (1), however, does not result in the formation of (2). Murov and Hammond measured the rate constants for the quenching of a series of aromatics by (2). In order to gain an understanding of the quenching process, they looked for relationships between k_q and several properties of the aromatics. No good correlation could be found with the electron affinity, ionization potential or singlet energy of the aromatics. They proposed a mechanism in which (2) is converted to (1) by way of vibrationally excited states (Scheme I).

Scheme I

$$\text{Sen} \longrightarrow {}^1\text{Sen}^*$$

$${}^1\text{Sen}^* + 2 \rightleftharpoons {}^1(\text{Sen}\cdots 2)$$

$${}^1(\text{Sen}\cdots 2) \longrightarrow \text{Sen}^{(v)} + 2^{(v)} \qquad \text{vibrational excited states}$$

$$2^{(v)} \longrightarrow 1$$

Weller and co-workers[6] questioned the mechanism proposed by Murov and Hammond. If quenching can occur by a vibrational mechanism, then any molecule of moderate complexity should be an effective fluorescence quencher. Weller believed the quenching and isomerization were occurring by an electron transfer mechanism.

The free energy relationships for electron transfer involving excited states have been thoroughly investigated by Weller.[7] The free energy for electron-transfer to or from excited state sensitizers can be calculated according to equation 1.

$$\Delta G = 23.06\,[E(D/D^+) - E(A^-/A) - \frac{e_o^2}{\varepsilon_a}] - \Delta E_{o,o} \qquad (1)$$

In this equation $E(D/D^+)$ is the oxidation potential of the electron donor, and $E(A^-/A)$ is the reduction protential of the electron acceptor. A term for the free energy gained by bringing two radical ions to encounter distance a in a solvent of dielectric constant ε is also included in the equation. $\Delta E_{o,o}$ is the energy required to excite an electron from the zero vibrational level of the ground state to the zero vibrational level of the lowest excited state of the sensitizer. The equation can be simplified if we consider only the case where the sensitizer acts as the electron acceptor. When a series of sensitizers are used with the same electron donor and the same solvent the free energy is given by equation 2.

$$\Delta G = \text{const} - [\Delta E_{o,o} + 23.06\ E(A^-/A)] \qquad (2)$$

The term $[\Delta E_{o,o} + E(A^-/A)]$ is the electron affinity of the excited state sensitizer. When the quenching constants of Murov and Hammond are plotted according to this relationship, a good correlation is observed (Figure 1).

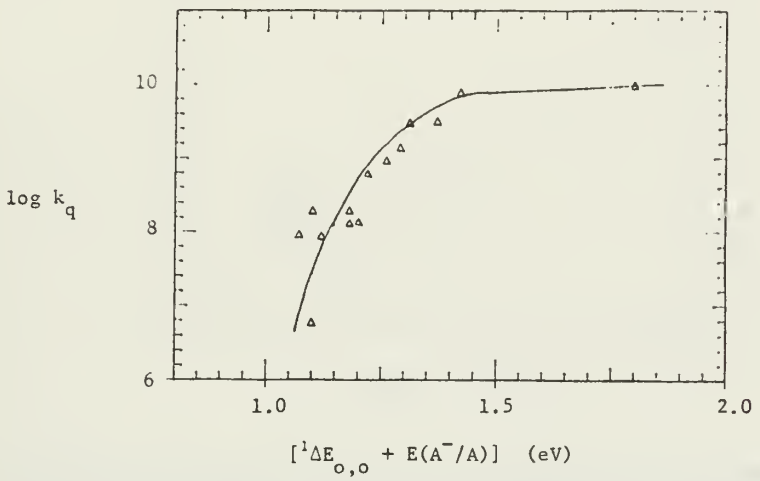
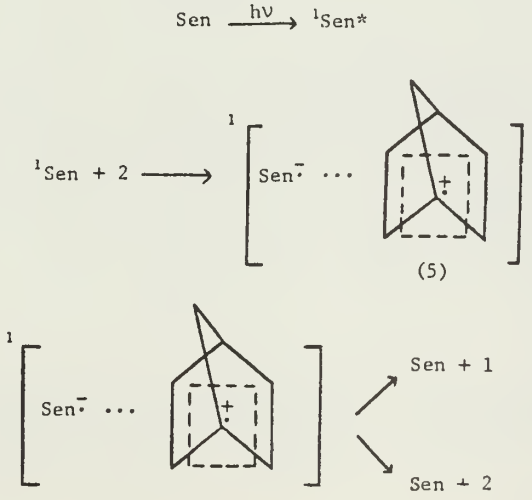


Figure 1. Correlation between rate constants of fluorescence quenching by (2) and electron affinities of excited sensitizers.

It has also been shown that the fluorescence of some sensitizers is quenched at a diffusion controlled rate by (2).[8] These sensitizers include 1,4-dicyanobenzene, 1-cyanonaphthalene, and 9,10-dicyanoanthracene. Excited state cyano-substituted aromatics are known to be particularly efficient electron acceptors.

The overall mechanism proposed by Weller is shown in Scheme II. Interaction between the excited singlet state of the sensitizer and (2) results in the formation of an exciplex with considerable charge-transfer character. Back electron transfer can result in regeneration of (2) or isomerization to (1). Weller noted that the mass spectra of (1) and (2) are identical.[9] He therefore proposed that a radical cation such as (5) is the intermediate that is formed.

Scheme II



A study by Gassman and co-workers[10] supports the idea that strained hydrocarbons can quench the fluorescence of aromatics by a charge-transfer mechanism. They measured the oxidation potentials of a series of strained hydrocarbons and found a good correlation with the rate at which they quench the fluorescence of naphthalene (Figure 2).

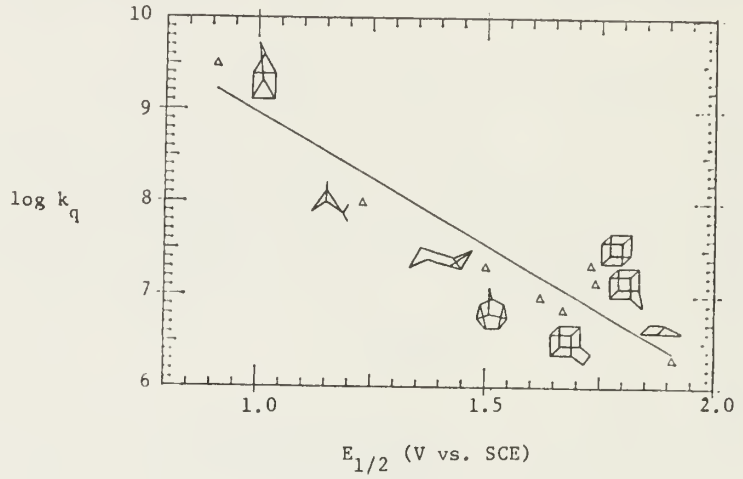


Figure 2. Plot of log k_q for quenching of naphthalene fluorescence vs. oxidation potentials of a series of strained hydrocarbons.

Triplet Quenching

In order to observe reactions of triplet excited states, flash photolysis or pulsed radiolysis techniques must be employed. A short time after the initial excitation pulse, an electronic transition to a higher triplet state can be observed. This triplet-triplet absorption is usually present in the visible region of the spectrum.

Barwise and Gorman[11] used pulsed radiolysis to study reactions of several triplet photosensitizers with (1), (2), (3) and (4). They found a good correlation between the triplet energy of the sensitizer and the rate constant for quenching of the triplet by (1) and (3) (Figure 3).

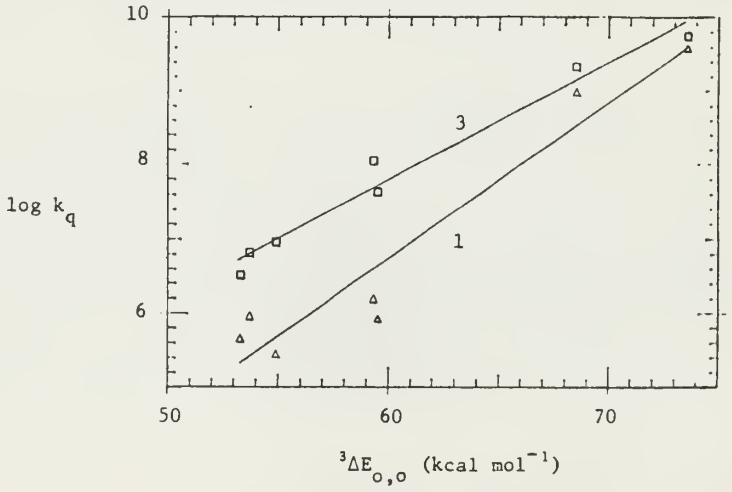


Figure 3. Correlation between rate constants for quenching of triplets by (1) and (3), and the triplet energy of the sensitizers.

This is exactly the result we would predict for simple electronic energy transfer from the sensitizer to (1) or (3). No correlation exists between log k_q and $^3\Delta E_{o,o}$ for (2). However, when a plot of log k_q versus $[^3\Delta E_{o,o} - E(A^-/A)]$ is made, a relationship becomes apparent (Figure 4). This observation is consistent with charge transfer from (2) to the excited triplet state of the sensitizer.

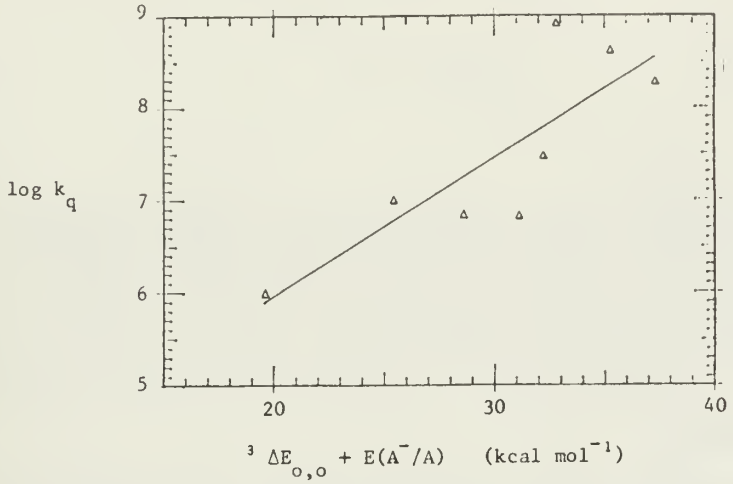


Figure 4. Correlation between rate constants of triplet quenching by (2) and electron affinities of excited sensitizers.

A known triplet electron acceptor, chloranil, has also been used as a sensitizer for (2).[8] In addition to the rapid quenching of the triplet-triplet absorption at 510 nm, a new transient absorption appears at 450 nm which has been assigned to the chloranil radical anion. Thus it appears from studies of fluorescence and triplet quenching that electron transfer can occur from (2) to both singlet and triplet excited states.

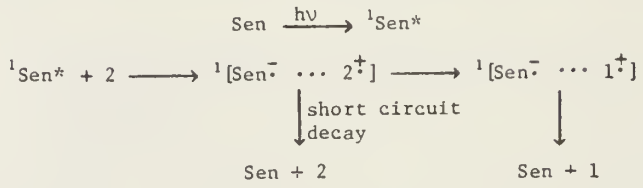
Solvent Effects

Studies of solvent effects have provided information about the nature of the exciplex formed from the interaction of (2) with the excited sensitizer. Jones and co-workers[8] measured the quantum yield for (2) $\longrightarrow$ (1) isomerization under conditions of 90-95% singlet quenching. They found that the quantum yields decreased rapidly as the solvent polarity was increased. Efficiencies in cyclohexane, dioxane, acetonitrile, and 80% acetonitrile/water were 0.71, 0.15, 0.095 and 0.049 respectively. Since quenching is occurring to a large extent without isomerization in polar solvents, energy loss by a non-radiative "short-circuit" path must be occurring.

Jones proposes that quenching in non-polar solvents involves close encounter with the sensitizer. This "collision" mechanism results in efficient ring opening through bond order changes induced in the polarized donor. On the other hand, in polar solvents electron transfer may occur by a relatively remote encounter between the sensitizer and (2), and not require the displacement of

all intervening solvent. Efficient back electron transfer results in a "short-circuit" decay of the ion pair (Scheme III).

Scheme III



The observation of ground state charge-transfer complexes provides evidence for exciplex formation.[12] The absorption spectrum of solutions of (2) and fumaronitrile or tetracyanobenzene show new red-shifted bands. Since fumaronitrile and tetracyanobenzene are strong electron acceptors, it has been proposed that the resulting complexes have a high degree of charge-transfer character. Irradiation of the complexes results in (2) ⟶ (1) isomerization.

Photoelectron Spectroscopy

Although it appeared clear that electron transfer was occurring from (2), further studies were necessary to determine the nature of the resulting radical cation. Weller proposed a single intermediate such as (5). However, other evidence suggests that discrete cations of (1) and (2) must exist.

Photoelectron spectra provide a unique means of classifying ions since the ionization bands are characteristic of the orbitals involved. Photoelectron spectra of (1) and (2) reveal two discrete cation states.[13] The existence of discrete cations is predicted by MINDO/3 calculations, which put the norbornadiene radical cation 13 kcal mol^{-1} lower in energy than the quadracycline radical cation.[14] On the other hand, γ irradiation of frozen solutions of (1) or (2) gives rise to a single species which has been assigned to the norbornadiene radical cation. This observation is not inconsistent with discrete ions. Calculations suggest that the activation energy for $(2^{+}\cdot) \longrightarrow (1^{+}\cdot)$ is small enought that $(1^{+}\cdot)$ may be the only stable species at 77°K.[14]

Chemically Induced Dynamic Nuclear Polarization (CIDNP)

The best evidence for discrete radical cations of (1) and (2) comes from recent CIDNP experiments.[15] The CIDNP method has proven to be a valuable tool for studying reactions proceeding via radical ion pairs.[16] In a typical CIDNP experiment, a sample is irradiated within the probe of an NMR spectrometer. Nuclear polarization results in the observation of enhanced absorption or emission of the NMR signals.

Roth and Schilling[15] used CIDNP to study the photosensitized isomerization of (1) and (2). When a solution of (1) and chloranil is irradiated in the NMR cavity, strongly enhanced absorption of the olefinic protons and weak emission of the bridge protons of (1) are observed (Figure 5a). No CIDNP signals are observed for the product (2). Results of earlier studies have shown that $(1^{+}\cdot)$ does not readily isomerize to form (2).

When a solution of (2) and chloranil are irradiated, CIDNP signals are observed for both (2) and the rearranged product (1), (Figure 5b). This is consistent with isomerization of the radical cation of (2). The observation of different polarization patterns in the reactions of (1) and (2) allow the unambiguous conclusion that two discrete radical cations are generated by charge-transfer from the two valence isomers.

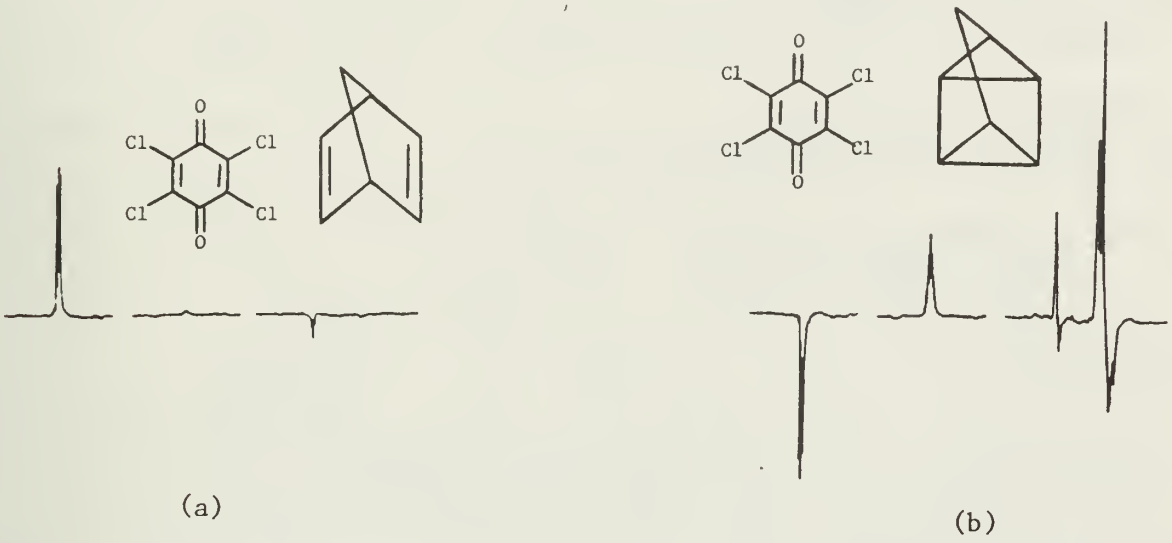


Figure 5. ^{1}H NMR observed during photolysis of chloranil with (1) (a), and with (2) (b).

Jones and co-workers recently found that when (3) is photolyzed in the presence of some polycyclic aromatic hydrocarbons CIDNP signals are observed for both (3) and (4).[17] They proposed a novel mechanism (Scheme IV) in which (3) becomes the electron acceptor.

Scheme IV

$$\text{Sen} \xrightarrow{h\nu} {}^1\text{Sen}^*$$

$${}^1\text{Sen}^* + 3 \longrightarrow {}^1[\text{Sen}^{+\cdot} \cdots 3^{-\cdot}]$$

$${}^1[\text{Sen}^{+\cdot} \cdots 3^{-\cdot}] \longrightarrow \text{Sen} + 3$$

$${}^1[\text{Sen}^{+\cdot} \cdots 3^{-\cdot}] \longrightarrow {}^3[\text{Sen}^{+\cdot} \cdots 3^{-\cdot}]$$

$${}^3[\text{Sen}^{+\cdot} \cdots 3^{-\cdot}] \longrightarrow \text{Sen} + {}^33^*$$

$${}^3[\text{Sen}^{+\cdot} \cdots 3^{-\cdot}] \longrightarrow {}^3\text{Sen}^* + 3$$

$${}^33^* \longrightarrow 4$$

They also found that the intensity of CIDNP signals and the quantum yields for isomerization were dependent on the triplet energy of the sensitizer.

When phenanthrene (E_T = 62 kcal mol^{-1}) is used, the CIDNP signals are strong and the quantum yield for (3) ⟶ (4) is 0.16. When anthracene (E_T = 43 kcal mol^{-1}) is used the CIDNP signal are 300-500 times weaker and the quantum yield is <.005. In both cases the rate of quenching of the aromatic fluorescence approaches the diffusion controlled limit.

Flash photolysis shows that in the case of phenanthrene, the triplet-triplet absorption is not observed when (3) is present. Instead a new absorption due to the phenanthrene radical cation is observed. In the case of pyrene (E_T = 48 kcal mol^{-1}), the triplet absorbance at 412 nm is observed in spite of the fact that >90% of the pyrene fluorescence is quenched by (3).

All of the observed results can be explained by the differences in the triplet energies of the sensitizers (Figure 6).

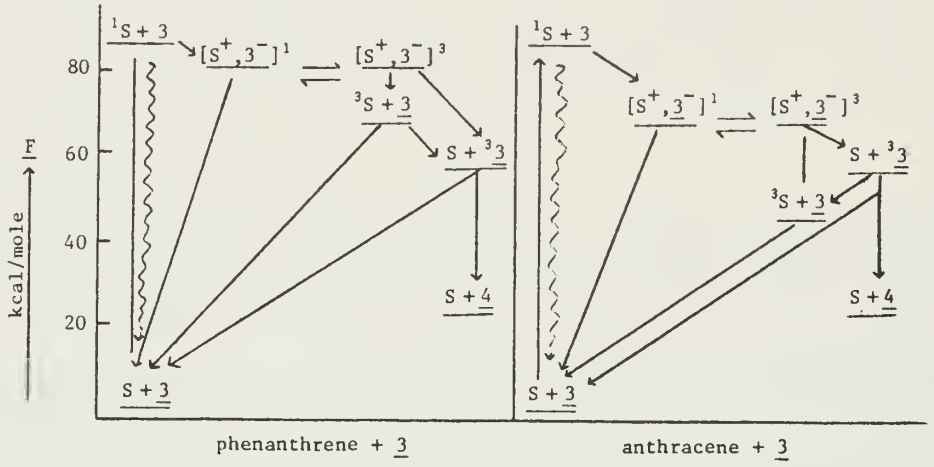


Figure 6. Energies of excited states and ion pairs of sensitizers with (3).

When back electron transfer occurs in the triplet ion pair, the triplet energy can be deposited in the triplet excited state of either (3) or the sensitizer. In the case of phenanthrene, the formation of triplet (3) is energetically more favorable, while in the case of anthracene or pyrene, deposition of energy in the sensitizer triplet state is more favorable. If the triplet excited state of (3) is formed, it can isomerize to (4). We have seen earlier that triplet (1) can isomerize to (2). The only difference here is the mechanism by which the excited triplet state of the norbornadiene is reached.

Conclusion

Photosensitized isomerizations of norbornadienes and quadricyclenes have been the subject of several mechanistic investigations by a variety of methods. All of the results show that the isomerization of (1) to (2), or (3) to (4), proceeds through the excited triplet state of (1) or (3). On the other hand, the reverse ring opening reaction (2) ⟶ (1) occurs by an electron-transfer mechanism. The radical cation of (2), resulting from charge transfer to the sensitizer, isomerizes to give the radical cation of (1). Back electron transfer gives the isomerized product (1).

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TOTAL STEREOSELECTIVE SYNTHESES OF THE (2R,4'R,8'R)-α-TOCOPHEROL (VITAMIN E) SIDE CHAIN

Reported by Jerry D. Clark March 3, 1983

Introduction

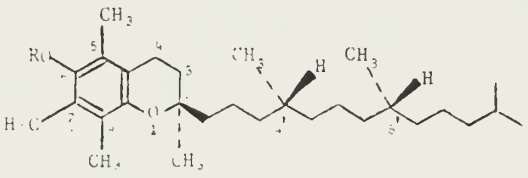
A dietary substance, first called factor X, necessary for the normal reproduction of rats was first recognized by Evans and Bishop[1] in 1923. In 1924, Sure[2] proposed that this substance be designated Vitamin E. Evans et al.[3] isolated the vitamin from wheat germ oil in 1936 and showed it to be an alcohol with marked biological activity. It is now recognized that Vitamin E is found almost exclusively in higher plants and is an essential nutrient of various vertebrates. Its absence may be associated with infertility, degenerative changes in muscle, or vascular abnormalities. The therapeutic value of Vitamin E in man is still controversial.

Biochemical Function

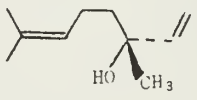
It is now generally accepted that Vitamin E (α-tocopherol) is an efficient inhibitor of lipid peroxidation and a free radical scavenger.[4] α-Tocopherol is believed to be located within the cell membrane as a complex with the polyunsaturated fatty acids of the phospholipids. The tocopherol may be specifically located near the membrane-bound enzyme complexes that can generate free-radicals. This position would facilitate the trapping of free-radicals by tocopherol and thereby prevent membrane damage.

Elucidation of Structure and Stereochemistry

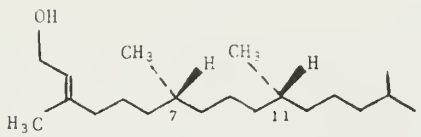
The structure of α-tocopherol was first correctly established by Fernholz[5] in 1938 via degradation studies using pyrolysis and chromic acid oxidation. Not until 1963 did Isler and co-workers[2] show that "natural" α-tocopherol (1) had a 2R,4'R,8'R configuration. They established this by correlating the asymmetry of natural α-tocopherol with (-)-linalool(2) with established R configuration[7e,f] and phytol (3) with 7R,11R configuration.[7a-d] The 4'R,8'R configuration of natural α-tocopherol derives from the fact that its



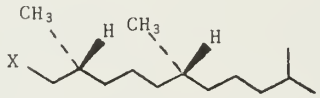
1a: R = H
1b: R = -COCH$_3$



2

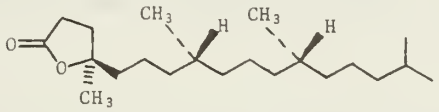


3

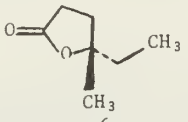


4a: X = -CH$_2$COCH$_3$
4b: X = -(CH$_2$)$_2$COCH$_3$
4c: X = -CHO
4d: X = -CH(CH$_3$)$_2$

oxidative degradation products -- 16-carbon ester 4a, 18-carbon ketone 4b, 15-carbon aldehyde 4c and the meso-hydrocarbon 4d -- are all identical in every respect to those substances prepared synthetically from (7R,11R)-phytol (3). The 2R-configuration follows by comparison of the molecular rotation of lactone 5 (from chromic acid oxidation of 1a) with that of δ-lactone 6 prepared from 2.

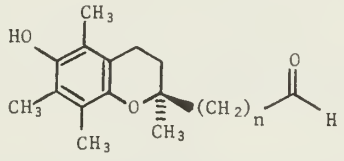


5



6

Additional proof was the total synthesis of (2R,4'R,8'R)-α-tocopherol[8] (1) from the (S)-(+)-formylchroman 6a.[11]

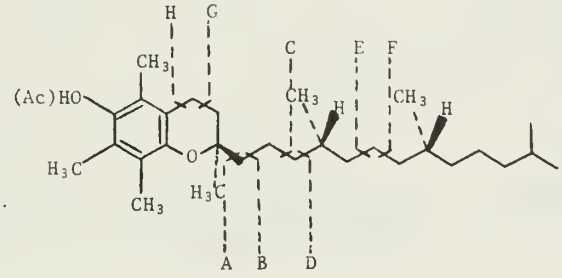


6a: n = 0
6b: n = 1

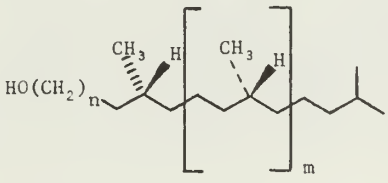
Synthesis

Analysis of the literature provides eight approaches by which an isoprenoid side chain intermediate and an appropriate hydroguinone or chromanol derivative have built the α-tocopherol carbon skeleton. These approaches are depicted in Figure 1. Of these approaches, only B,C,E and F lead to an "easy"

Figure 1.



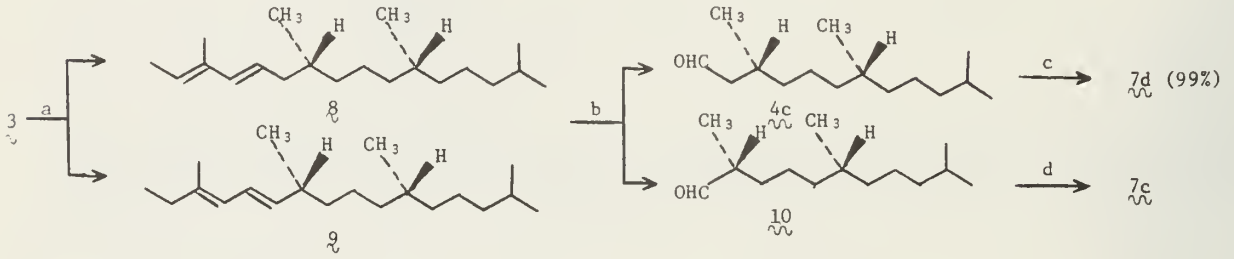
and unambiguous synthesis of 2R-(or 2S-)α-tocopherol. All other approaches[9] lead to mixtures of 2R,4'R,8'R and 2S,4'R,8'R-epimers. Therefore, the literature reports have concentrated upon synthetic routes to the optically active acyclic alcohols 7a-d.



	m	n
7a:	0	0
7b:	0	1
7c:	1	0
7d:	1	1

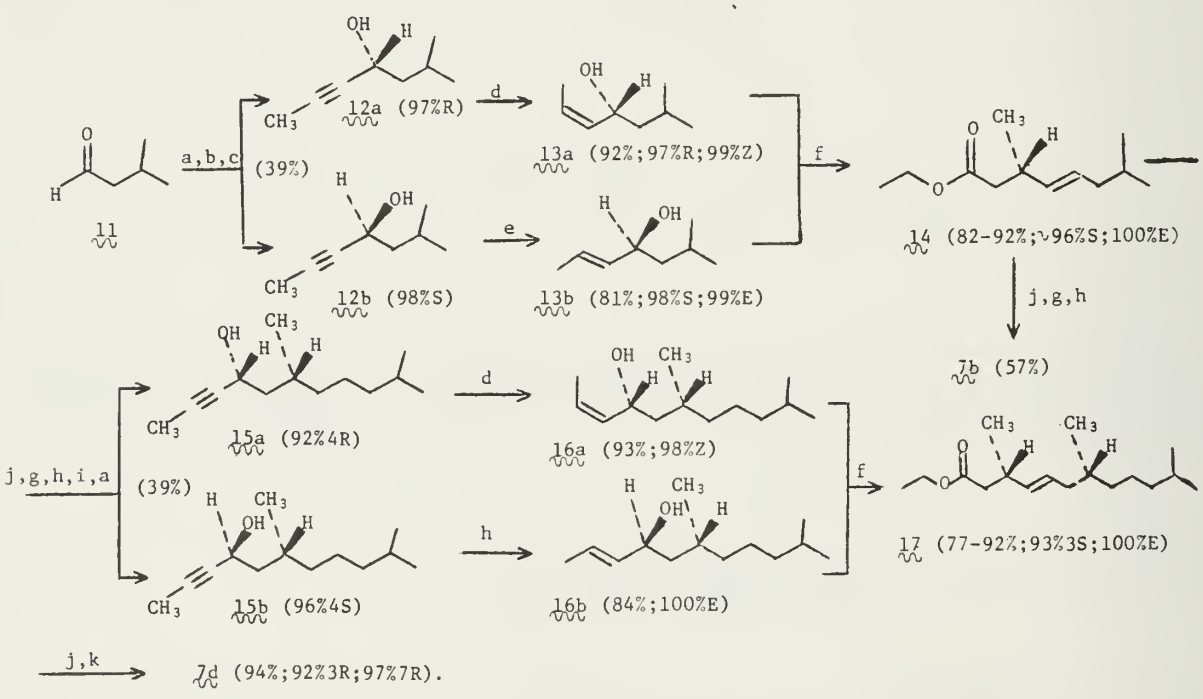
The first formal total synthesis of (2R,4'R,8'R)-α-tocopherol was by Isler and co-workers.[8] They took advantage of the known (7R,11R) configuration of natural phytol[7a-b] (3) to synthesize the 15-carbon alcohol 7d via aldehyde 4c (Scheme 1).

Scott et al.[10] utilized the 14-carbon alcohol 7c in their synthesis of (2R,4'R,8'R)-α-tocopheryl acetate (1b). They modified Isler's procedure (Scheme 1) by utilizing aldehyde 10 instead of 4c.

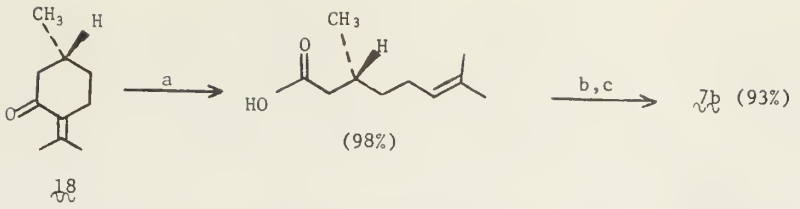


Scheme 1. (a) p-TsOH, phthalic anhydride (b) O_3, pentane, -50° (c) $LiAlH_4$ (d) $NaAlH_2(OCH_2CH_2OCH_3)_2$ (Red-Al).

Owing to the difficulty of obtaining natural phytol (3), Chan et al.[12a,14] sought an alternative method to synthesize a side chain alcohol intermediate from a simple and readily available starting material. They accomplished this by using isovaleraldehyde (11) via stereospecific 5-carbon homologation to synthesize both the 10-carbon (7b) and 15-carbon alcohol (7d) intermediates (Scheme 2). The key transformations in this synthetic sequence involves the conversion of allylic alcohols 13a and 13b to the ethyl ester 14 and, likewise, 16a and 16b to 17 via the ortho-ester variant of the Claisen rearrangement. Each transformation resulted in nearly 100% chiral transmission. An alternative synthetic approach to alcohol 7b via (R)-(+)-pulegone (18) is also reported[12] (Scheme 3).

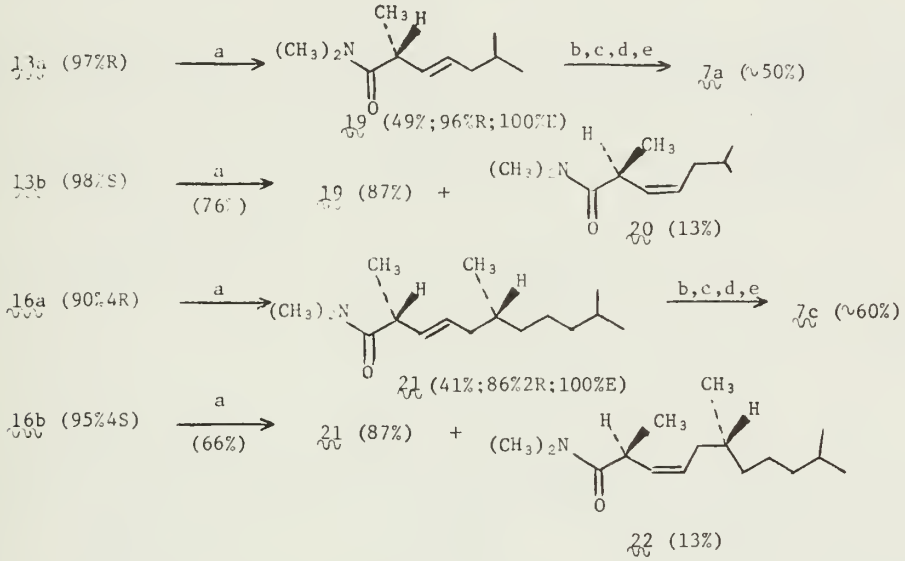


Scheme 2. (a) $H_3C-C\equiv C-MgBr$. (b) phthalic anhydride, py. (c) (S)- (-)- or (R)-(+)-α-methyl benzylamine, reflux. then 1N NaOH, reflux (d) H_2, Lindlar catalyst, quinoline, hexane, R.T. (e) Na, NH_3, -78°C → reflux. (f) $CH_3C(OEt)_3$, $CH_3CH_2CO_2H$. (g) 6N NaOH, MeOH, reflux (h) Red-Al. (i) silver carbonate on Celite, toluene. (j) H_2, 5% Pd(C), EtOAc (k) $LiAlH_4$, Et_2O, reflux.



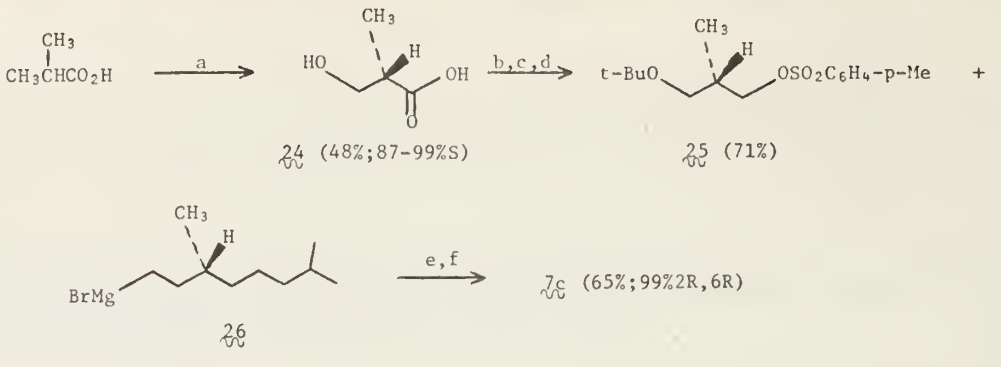
Scheme 3. (a) HCl (gas) then 5% $Ca(OH)_2$. (b) Red-Al. (c) Pd(C), H_2, EtOAc.

In an approach related to the Claisen rearrangement, Chan and Saucy[13] describe the synthesis of the alcohols 7a and 7b via [2,3] sigmatropic shifts. Reaction of the previously synthesized optically active (R,Z)-allylic alcohols 13a and 16a (see Scheme 2 for syntheses) respectively, with N,N-dimethylformamide dimethyl acetal proceeds stereoselectively to give (2R,E)-β,δ-unsaturated amides 19 and 21 (Scheme 4). In these two cases, chiral transmission was nearly 100%. However, (S,E)-allylic alcohols 13b and 16b provided a mixture of (2R,E)- and (2S,Z)-β,δ-unsaturated amides, from which the nearly optically pure (2R,E)-isomer could be isolated. The amides 19 and 21 were transformed into 7a and 7c, respectively.



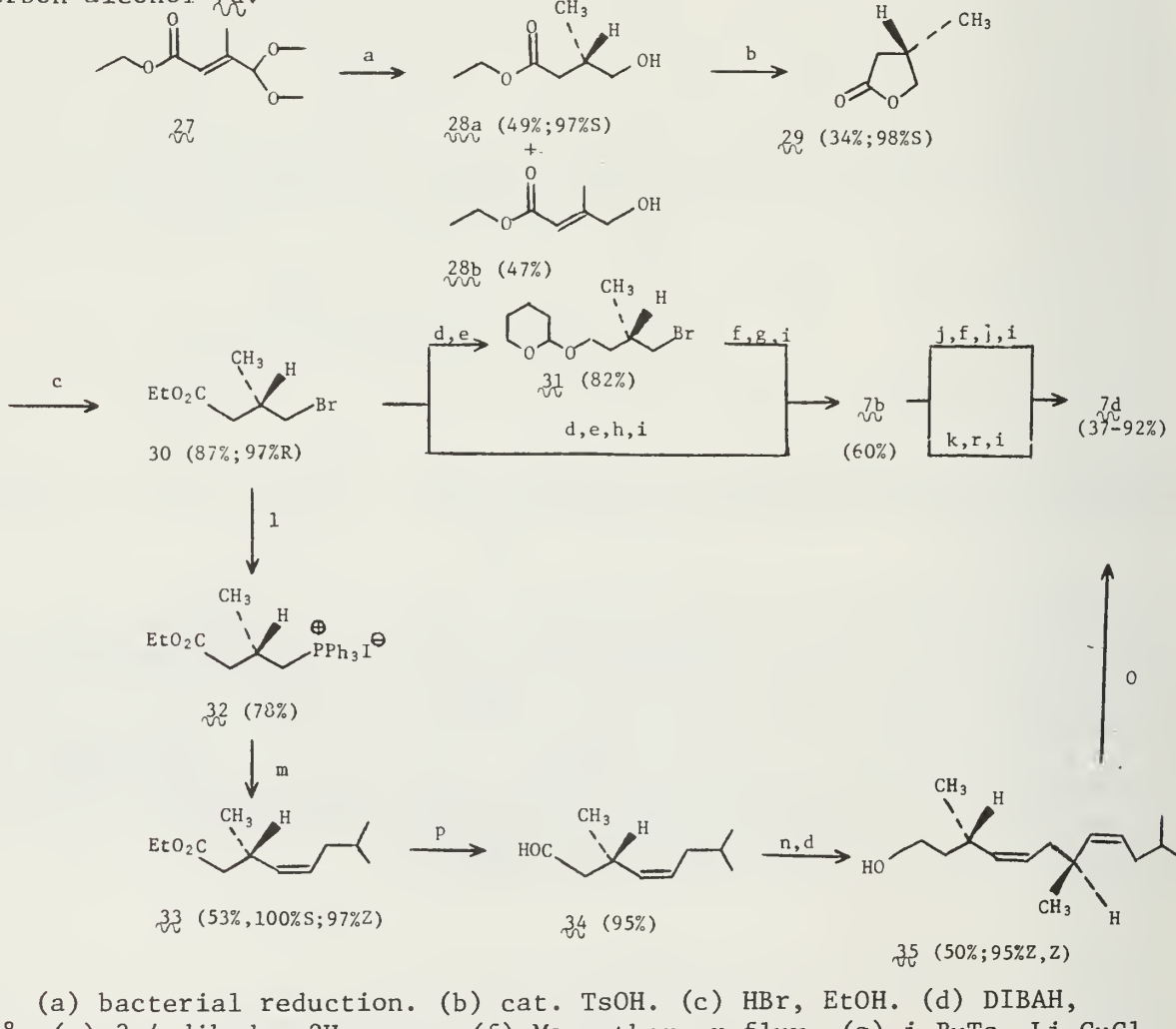
Scheme 4. (a) $(CH_3)_2NCH(OCH_3)_2$ (b) 5% Pd(C), H_2, EtOAc (c) conc. HCl, reflux. (d) CH_2N_2 Et_2O, R.T. (e) $LiAlH_4$, Et_2O, reflux.

The first use of a microbiologically derived, optically active side chain synthon toward the synthesis of one or more of the alcohol intermediates (7) is reported by Cohen et al.[15a-c,16] In their synthesis of alcohol 7c, they used a procedure by Goodhue and Schaeffer[15d] to oxidize isobutyric acid (23) to (S)-(+)-3-hydroxy-2-methyl propanoic acid (24) via the bacteria, Pseudomonas putida. In the most expeditious approach by Cohen, coupling of the tosylate with the Grignard 26 (itself derived from (R)-(+)-pulegone (18; see Scheme 3) followed by bromination with Ph_3P, NBS and then formation of the Grignard) leads to the 14-carbon alcohol 7b after deprotection (Scheme 5).

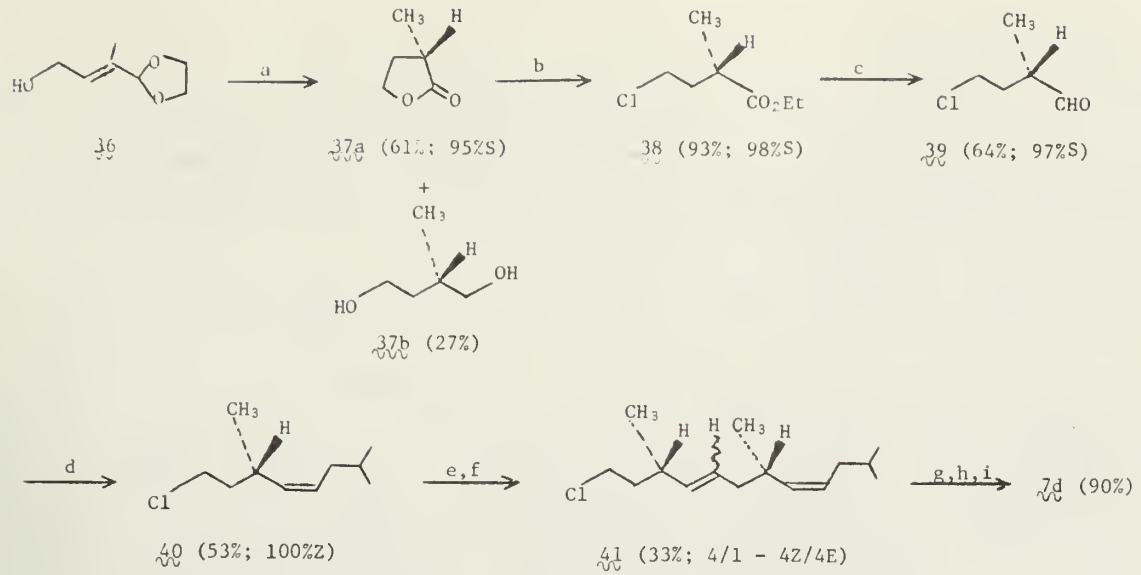


Scheme 5. (a) Bacterial oxidation. (b) isobutylene, H_3PO_4, BF_3-Et_2O. (c) $LiAlH_4$, Et_2O. (d) p-CH_3-C_6H_4-SO_2Cl, py.(p-TsCl.) (e) -78° → R.T., Li_2CuCl_4. (f) CF_3CO_2H, 0

In a series of reports, Zell et al.[17a,c] and Schmid and Barner[17b] described the synthesis of the 10-carbon side chain 7b (Scheme 6) and the 15-carbon side chain 7d (Scheme 6 and 7) via the microbiologically derived 5-carbon lactones 29 (Scheme 6) and 37a (Scheme 7). The two key compounds were prepared by fermentative transformation including the enantioselective hydrogenation of the double bond of the methyl crotonate 27 by bakers yeast, Saccharomyces cerevisiae (yielding 29 after ester hydrolysis and cyclization of the fermentation product 28a) and the (E)-butenol 36 by the fungus Geotrichium candidum (yielding 37a directly). In Scheme 6, the S-3-methyl lactone 29 is used via the ester 30 in a sequence of either of two Grignard coupling pathways or two consecutive Wittig reactions to ultimately synthesize 7d. In Scheme 7, the 5-carbon lactone 37a is used via ester 38 in two successive Wittig reactions to again construct the 15-carbon alcohol 7d.



Scheme 6. (a) bacterial reduction. (b) cat. TsOH. (c) HBr, EtOH. (d) DIBAH, Hexane, 0°. (e) 3,4-dihydro-2H-pyran. (f) Mg, ether, reflux. (g) i-BuTs, Li_2CuCl_4. (h) i-BuMgBr, Li_2CuCl_4. (i) 7N HCl. (j) Ph_3P, NBS. (k) p-TsCl, py. (l) NaI, ethyl methyl ketone then Ph_3P. (m) NaH, DMF, 11. (n) NaH, DMF, 32. (o) Raney-Ni, H_2, EtOAc. (p) DIBAL, Hexane, -70° (q) 31, Li_2CuCl_4. (r) Grignard of 31, Li_2CuCl_4.



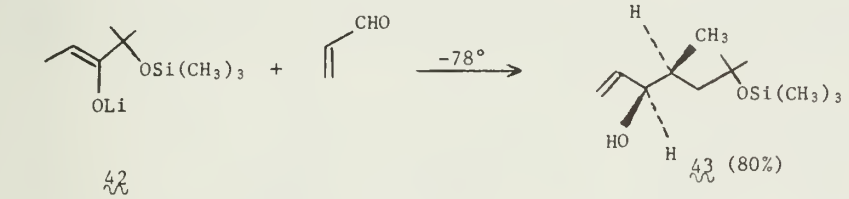
36 37a (61%; 95%S) 38 (93%; 98%S) 39 (64%; 97%S)

37b (27%)

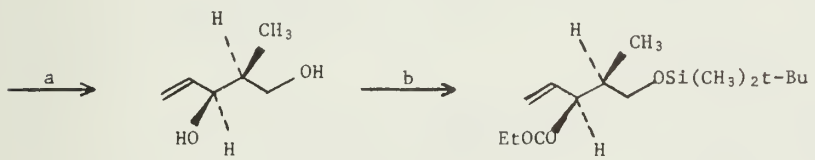
40 (53%; 100%Z) 41 (33%; 4/1 - 4Z/4E)

Scheme 7. (a) bacterial reduction (b) HCl/EtOH. (c) DIBAH, Hexane, -70%. (d) isobutyl triphenyl phosphonium bromide, Et_2O. (e) Ph_3P, DMF, reflux. (f) NaH, DMF, 39. (g) PtO_2, H_2. (h) DMF, calcium acetate (i) 4N NaOH.

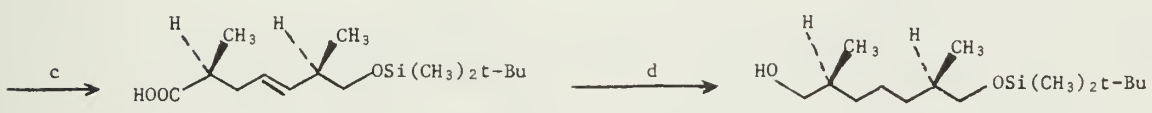
Recently, Heathcock and Jarir[18] stereoselectively synthesized the 14-carbon alcohol 7c (Scheme 8). They used the 1,2-stereoselction of the aldol condensation of the lithium enolate 42 with acrolein to generate the asymmetric center at C_2 of 7c. Subsequent Claisen rearrangement of the propionate ester 45 to the unsaturated acid 46 generated the C_6 asymmetric center.



42 43 (80%)



44 (90%) 45 (73%)

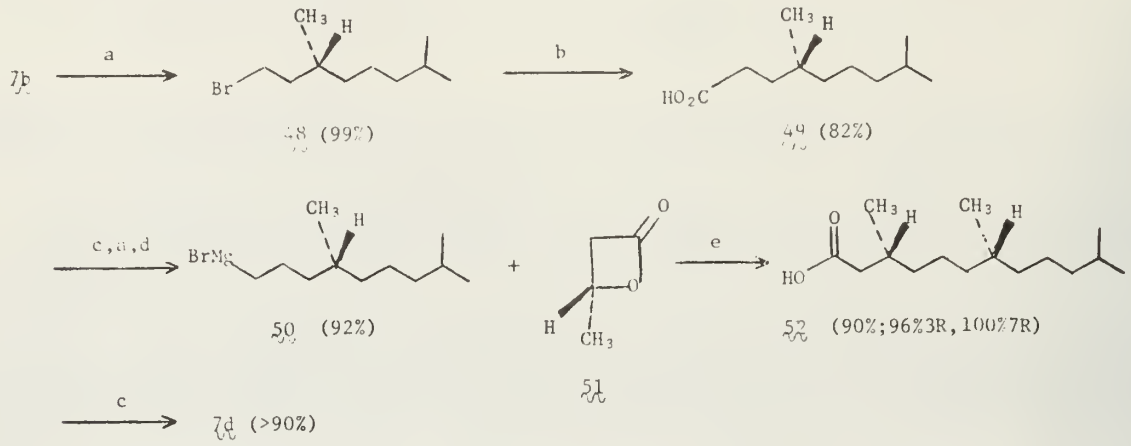


46 (58%) 47 (83%)



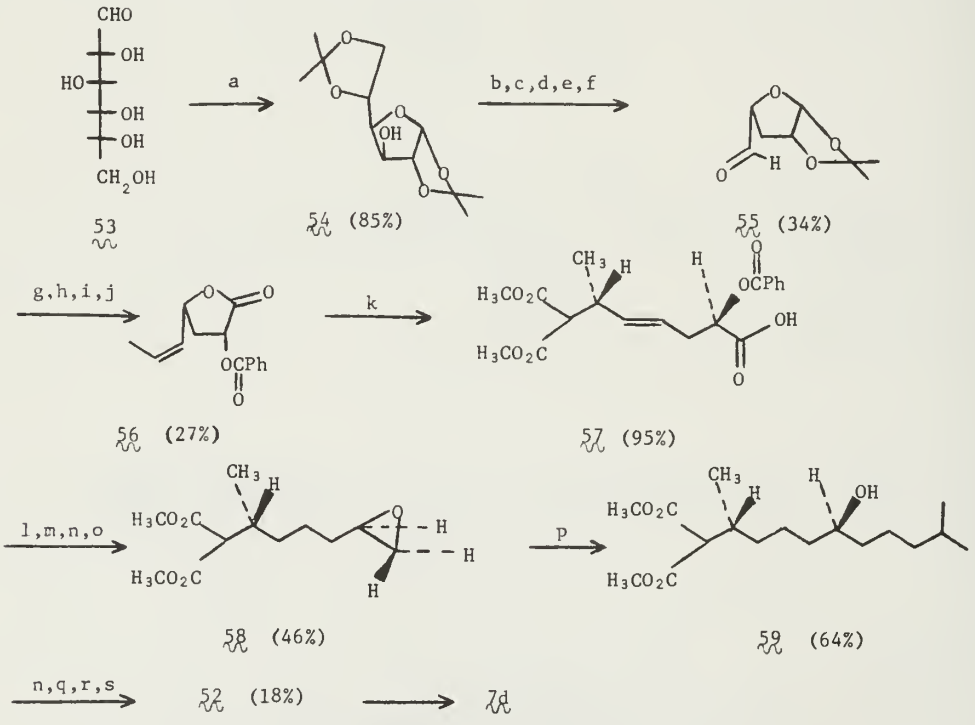
Scheme 8. (a) H_5IO_6, THF then $LiAlH_4$, THF, reflux. (b) Et_3N, t-$Bu(CH_3)_2SiCl$, 4-(N,N-dimethylamino)-pyridine, CH_2Cl_2 then propionyl chloride, CH_2Cl_2. (c) LDA, THF, -78° then t-$Bu(CH_3)_2SiCl$, -78° then 25°. (d) H_2, PtO_2, EtOAc then B_2H_6, THF, 25°. (e) p-TsCl, py., CH_2Cl_2 then i-BuMgBr, Li_2CuCl_4, THF, 0° → 25° then n-$Bu_4N^+F^-$, THF.

Fujisawa et al.[19a] have reported the total synthesis of optically active (7R,11R)-phytol (3). Intermediates toward this total synthesis were alcohols 7b and 7d. The C_7 asymmetric center of 7d was derived from (R)-(+)-pulegone via 7b (see Scheme 3) and, as illustrated in Scheme 9., the C_3 asymmetric center from an S_N2-type ring-opening of (R)-(+)-β-methyl-β-propiolactone (51; derived from (S)-(+)-3-bromobutyric acid.[19a]).



Scheme 9. (a) HBr, 115° (b) NaCN then $OH^{\ominus}$. (c) $LiAlH_4$. (d) Mg, Et_2O, reflux. (e) CuI, THF-$(CH_3)_2S$, -20° then 50 then R.T.

In a novel synthesis, Trost and Klun[20] used D-glucose (53) as the requisite substrate to construct the 15-carbon methoxy ester 52 (Scheme 10) which may be converted to 7d. Two key transformations are utilized. The first is the palladium catalyzed regioselective alkylation of the lactone 56 to 57. The second key transformation is the organocyprate epoxide opening of 58 to 59.



Scheme 10. (a) $ZnCl_2$, H_3PO_3, acetone, R.T., 3 days. (b) 1.5 equiv. TsCl, py. (c) KOH, 0.4mm, 60°C. (d) H_2, 3 atm., 10%Pd(C), EtOH. (e) cat. HCl, 1:1 MeOH/H_2O. (f) 1.2 equiv. $NaIO_4$, H_2O(pH 6-7). (g) $Ph_3P^{\oplus}CH_2CH_3Br^{\ominus}$, KOt-Bu, THF. (h) cat. TsOH, 10:1 CH_3CN, H_2O. (i) 1.5 equiv. Ag_2CO_3/celite. (j) PhCOCl, py., CH_2Cl_2. (k) 1.3 equiv. sodiomalonate, 5% $Pd(PPh_3)_4$, THF. (l) H_2, 1 atm. PtO_2, EtOAc. (m) 5 equiv. $BH_3 \cdot S(CH_3)_3$, Et_2O. (n) 2.2 equiv. TsCl, py. (o) 2.2 equiv. $NaOCH_3$, CH_3OH. (p) isopentyl copper cyanide, Et_2O, -10°C. (q) 5 equiv. $Li(CH_3)_2Cu$, Et_2O, -15°C. (r) KOAc, DMSO, 140°. (s) KOH, 4:1 MeOH:H_2O.

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ALUMINUM CHLORIDE AND BROMIDE COMPLEXES OF CYCLOBUTADIENES

Reported by Don Champion March 10, 1983

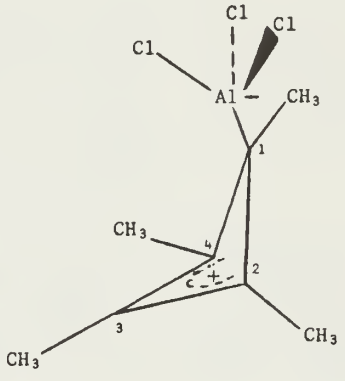
Interest in aluminum chloride complexes of cyclobutadienes stems from the discovery that the action of aluminum chloride on 2-butyne can be used for the synthesis of hexamethylbenzene[1] or octamethyl-syn-tricyclo[4.2.0.0^{2,5}]-octa-3,7-diene.[2] Further investigations have clarified the nature of cyclobutadiene-aluminum chloride complexes and provided insight into their synthetic utility. Because of their similarity, both aluminum chloride and aluminum bromide complexes will be discussed.

Preparation

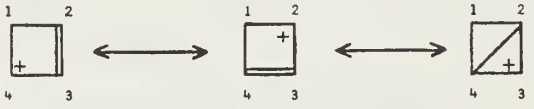
Aluminum chloride and bromide complexes are prepared by mixing the appropriate alkynes and aluminum halides in anhydrous, non-nucleophilic solvents. The first cyclobutadiene-aluminum chloride complex was prepared from 2-butyne and aluminum chloride in dichloromethane.[3] Subsequently, ring fused compounds were formed by the action of aluminum chloride on diynes.[4] The method can be broadened to include some terminal alkynes and cross coupling reactions of 2-butyne with terminal alkynes.[5,6] In these cases, aluminum bromide is used to avoid side reactions caused by aluminum chloride.

Properties

The aluminum halide complexes are stable in solution. An X-ray structure determination of 1[7] reveals a carbon-aluminum sigma bond and a short transannular C_2-C_4 distance accompanied by ring puckering. An explanation of the latter two phenomena is provided by invocation of a homocyclopropenium contribution (2c) to the resonance hybrid. Indeed, the complex has been used as a model of the homocyclopropenium ion.[8]



1



2a 2b 2c

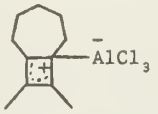
Perhaps the best method for determining the extent of the contributions of 2a and 2b vs. 2c is ^{13}C NMR. Olah and coworkers[9] conclude the contribution of the cononical forms can be measured qualitatively by the difference in the chemical shifts of C_2 and C_4 vs. C_3. For example, in complex 1 the shifts of C_2 and C_3 are similar whereas the resonances of C_2 and C_3 in the cyclobutenylium cation differ by 54 ppm and C_3 is downfield of C_2. This indicates the contribution of 2c is less important for 1. However, contributions due to rehybridization and paramagnetic shielding may also effect the chemical shifts.

An interesting phenomenon is displayed in a variable temperature NMR study[4b,10] of the aluminum chloride complexes. At -10° the ^{1}H NMR spectrum of 1 shows three different methyl groups which become equivalent on warming.

Calculation of the activation energy gives E_a= 20.3 kcal mol^{-1}. By measuring rate constants the process was identified as aluminum chloride migration via 1,2 shifts. Study of 3 shows the rate of migration to be 2100 times slower while 4 shows similar behavior to 1. The difference is ascribed to strain imposed by the 6-membered ring in one conformation of 3.



3



4

Some insight into the interaction of 2-butyne and aluminum bromide can also be ascertained from an NMR experiment.[5] Exchange of 2-butyne and another species believed to be a 2-butyne-aluminum bromide adduct is apparent at -100°.

Synthetic Utility

Cyclobutadiene complexes of aluminum chloride and bromide provide a simple method for one pot synthesis of several compounds. Hexamethylbenzene,[1] Dewar benzenes,[1,3,11-13] octamethyl-syn-tricyclo[4.2.0.$0^{2,5}$]octa-3,7-diene,[2,10] bicyclo-[2.2.0]hex-2-enes,[3,14] pyridines,[6,11,15] Dewar pyridones[16] and pyridones[16] may be produced using cyclobutadiene-aluminum halide complexes as intermediates. In addition, information on the reaction of the complexes with methyl- and phenyl-isocyanate,[17] di-tert-butyl- and diphenylcarbodiimide,[17] N-sulfinylaniline,[17] cyclohexylisonitrile[11] and sulfur dioxide[11] is available.

Summary

In conclusion, cyclobutadiene-aluminum halide sigma complexes are interesting because of their dynamic behavior. Their ease of preparation facilitates their use as cyclobutadiene synthetic equivalents in some instances. Perhaps further investigations will broaden their application in synthesis in the future.

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THE LANTHANIDE ELEMENTS IN ORGANIC SYNTHESIS

Reported by Thomas L. Fevig March 14, 1983

Aside from Ce(IV) oxidations[1] and NMR studies,[2] the lanthanide elements ($^{57}La \rightarrow {}^{71}Lu$) have received very little attention from organic chemists. However, they possess certain electronic and stereochemical properties which are unique, and therefore, of potential utility. For example, the ionic radii of the lanthanides are considerably larger than those of the transition metals, and there is a smooth decrease in size across the series. The large size results in large coordination numbers, typically from seven to eleven, and this in turn leads to unusual coordination geometries. In addition, the overwhelmingly preferred oxidation state of the lanthanides (Ln) is +3. It is this preference which leads to the strong reducing power of Ln^0 and Ln^{+2} species, and the oxidizing strength of Ln^{+4} reagents. Finally, these elements are unusual in that the possibility of f-orbital participation in bonding exists.[3]

Although the use of the lanthanides in organic synthesis has been, for the most part, sporadic, in recent years some more systematic work has been done. These studies have dealt mainly with two types of lanthanide reagents: 1) the trivalent salts, and 2) the Ln^{+2} salts. Herein will be reported the major synthetic transformations possible with each of these reagent types. The advantages and disadvantages of these methods will be discussed, and comparisons will be made with existing methodology. Finally, for some of the more interesting examples, mechanistic interpretations will be presented.

The Trivalent Lanthanides

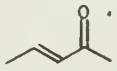
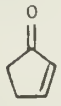
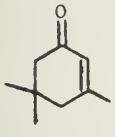
Luche and coworkers have done much of the work on the use of Ln^{+3} reagents in carbonyl chemistry. One problem they have studied is the 1,2 reduction of α,β-unsaturated ketones.[4] A number of reagents, such as alkyl or alkoxy aluminum hydrides or borohydrides, AlH_3, $NaBH_3CN$, and zinc complex reducing agents, have been introduced recently which offer good selectivity in this reaction.[5] However, these reagents usually suffer from one or more limitations. For example, many are not effective for substrates, such as cyclopentenones, which are particularly prone to 1,4 reduction. Many others are not selective for ketones. Also, the bulky reagents are sensitive to steric hindrance. Finally, many of the reagents are either costly or inaccessible, or require rigorous protection from moisture and air. Luche's investigations were prompted by these difficulties and by the following observations. First, it has been shown by NMR studies that Ln^{+3} shift reagents can modify the conformation, and thus the reactivity of some flexible ketones.[6] Second, many workers have modified the reducing properties of $NaBH_4$ by the addition of various metal salts to the reaction medium.[7] Third, molecular orbital calculations have shown that lithium and sodium ions alter the electron density of an enone, making the carbonyl carbon more reactive toward nucleophiles, and the β carbon less so.[8] The lanthanides, by virtue of their superior coordinating ability, were expected to enhance the reactivity of the carbonyl carbon to an even greater extent.

That Ln^{+3} salts do have a large effect on the regioselectivity of $NaBH_4$ enone reductions is borne out experimentally. A wide variety of substrates give exclusively the allylic alcohol in very high yield, and even cyclopentenones are reduced with excellent selectivity. Some representative examples are

shown in Table I.

Table I.

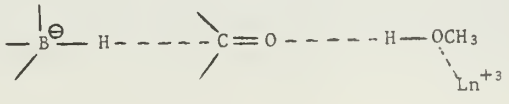
Enone reductions with $NaBH_4$

	Substrate	Lanthanide (III)	% Yield	allylic alcohol/saturated alcohol
1)		none	100	89/11
		Ce	100	100/0
2)		none	100	0/100
		Sm	100	94/6
		Ce	100	97/3
3)		none	100	51/49
		Sm	98	93/7
		Ce	100	>99/trace
4)		Ce	100	100/0
5)		none	98	90/10
		Ce	100	100/0

Several aspects of this reduction system are noteworthy. The reaction is simple to perform and the conditions are mild. Since small amounts of water have little effect on the yield or regioselectivity, the commercially available $LnCl_3$ hexahydrates can be used. Also, the reduction is quite selective for ketones and can be conducted over a wide pH range. Furthermore, the reduction is relatively insensitive to steric hindrance (entry 4, Table I), and is very fast. Unfortunately, stoichiometric quantities of the lanthanide are required for optimum results.

It was of interest to determine the function of the lanthanide in the reduction. Two possibilities were considered initially. The high reaction rate and regioselectivity could result from the formation of a more reactive reducing agent such as $Ln(BH_4)_3$, or from the formation of a more reactive carbonyl via complexation with the Ln^{+3} ion. The first possibility was refuted by preparing several borohydrides such as $Ln(BH_4)_3$ and $LnCl(BH_4)_2$, and subsequently using them to reduce cyclohexenone. In THF the reduction was not regioselective, while in methanol decomposition of the reagent was faster than reduction. The complexation theory cannot be dismissed so easily. In fact, this mechanism is supported by the observation that, in THF, Ln^{+3} salts give excellent results whereas the use of other ions (which do not complex so well) gives low yields and very poor regioselectivities. However, when the reaction is run in methanol, complexation of the ketone is not likely since the lanthanides are known to complex more readily with alcohols than with ketones.[9] Based on this knowledge, Luche has proposed that the function of the lanthanide is to complex with the methanol, thereby creating a more strongly acidic medium. This is illustrated in Scheme I.

Scheme I.

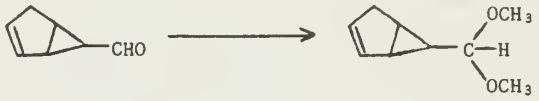


Experimental results are in agreement with this proposal. Dilution of the reaction mixture with methanol, which would facilitate methanol/Ln^{+3} complexation while suppressing that between lanthanide and ketone, results in an increase in 1,2 selectivity.

While the complexation depicted in Scheme I may contribute to the increased selectivity and reaction rate, the structure of the reducing species could also be important. As mentioned above, $LnCl(BH_4)_2$ and $Ln(BH_4)_3$ can be ruled out. Also, reduction by a transient Ln^{+2} species is unlikely since these react poorly with ketones.[10] Several experiments have implicated sodium alkoxyborohydrides as the reducing agents.

When $NaBH_4$ is added to an alcohol, H_2 is evolved and alkoxyborohydrides are formed.[11] This reaction is greatly accelerated in the presence of Ln^{+3} salts. Methanol gives a very fast reaction, ethanol somewhat slower, and the reaction is quite slow in 2-propanol. Since enone reductions in 2-propanol are slow and give poor regioselectivity, this may be regarded as evidence that alkoxyborohydride formation is the first step in the reduction. Additional data lend support. Alkoxyborohydrides are known to be more reactive than $NaBH_4$[12] and this could, in part, explain the high reaction rate observed. Also, when reductions are performed in THF with $NaBH(OMe)_3$ and Ce^{+3}, the results are very similar to those obtained with $NaBH_4/Ce^{+3}$/methanol. Thus, when methanol is the solvent, the lanthanide appears to play a dual role of complexing with the solvent and catalyzing the formation of methoxyborohydrides. Conversely, in THF the lanthanide induces 1,2 selectivity by complexing with the ketone.

Luche and coworkers have also found Ln^{+3} ions to be efficient catalysts for the formation of acetals.[13] These important carbonyl protecting groups are usually prepared in the presence of catalysts such as protic acids, $FeCl_3$, NH_4NO_3, BF_3 or, more recently, resins doped with trialkyl orthoformates.[14] While these methods are often quite acceptable, lanthanide catalysis offers certain advantages. For example, near quantitative yields of dimethyl acetals are obtained at room temperature in methanol. Also, the reaction is complete in 10 min., making this method useful for the acetalization of acid sensitive compounds. In the case of bicyclo[3.1.0]-hex-2-ene-6-carboxaldehyde 1 for instance, using H_2SO_4 or p-toluene sulfonic acid gives rearrangement products, whereas Ce^{+3} catalysis produces the dimethyl acetal 2 in 95% yield.



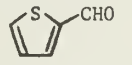
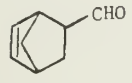
1 2

Although mechanistic work has not been done on this reaction, carbonyl activation by a scheme analogous to that described for enone reductions seems reasonable. Unlike the enone reductions however, the particular lanthanide used sometimes has a considerable effect on the results. As shown in Table II, the heavier (smaller) ions seem to be superior catalysts. This could be due to reduced steric hindrance or to the more acidic character of the smaller ions.

Another interesting feature of lanthanide catalysis is the selectivity observed. Aldehydes react readily to give the corresponding acetals, but ketones give ambiguous results. Often, no ketal is isolated from the reaction mixture. These findings suggest that selective acetalization of aldehydes in the presence of ketones might be possible. Indeed, competitive experiments have shown that this transformation is possible in many cases. When an aldehyde and a ketone are simultaneously subjected to the acetalization conditions

Table II.

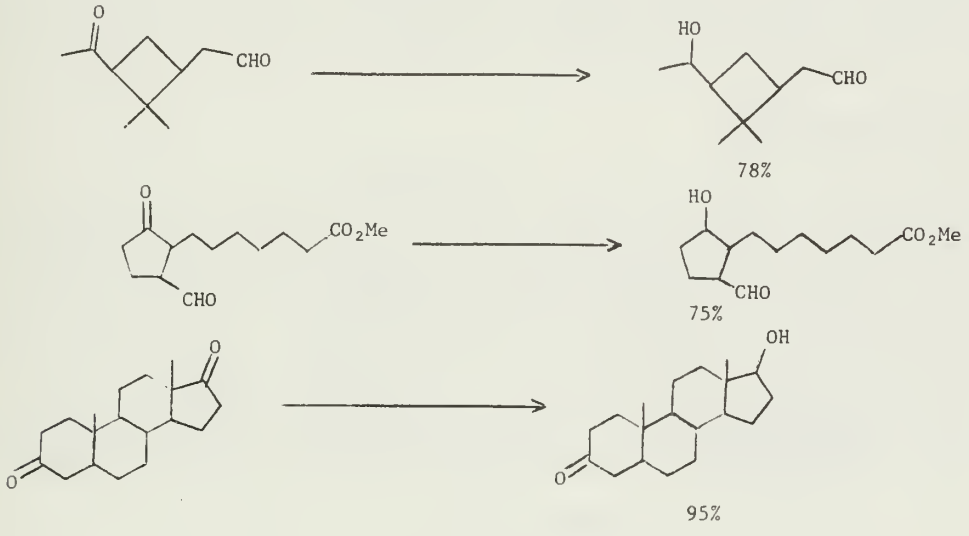
Acetalization with $LnCl_3$ catalysts

Aldehyde	% Yield $LaCl_3$	$CeCl_3$	$NdCl_3$	$ErCl_3$	$YbCl_3$
	95	95	95	95	100
PhCHO	85	90	90	100	
p-$MeOC_6H_4CHO$	60	70	80	95	
p-BrC_6H_4CHO		80		85	100
PhCH=CH-CHO		75	80	100	
	50	60		80	100
$C_5H_{11}CHO$	90	100		100	
	70	70		80	100

and then sequentially treated with $NaBH_4$ and HCl, a secondary alcohol and the starting aldehyde are recovered in high yields. Some selectivity is also obtained when two ketones are processed in this manner, though the nature of the carbonyl protecting species is not always clear.

From a synthetic point of view, this reaction sequence is of more interest when a bifunctional molecule is the substrate. Such experiments have been done, and few examples are shown in Scheme II.

Scheme II.



The net result of this procedure is the efficient, one-pot reduction of the less reactive carbonyl of a dicarbonyl compound. There are some limitations which should be pointed out. When carbonyl discrimination becomes difficult, the lighter lanthanides must be used since they are less effective catalysts and are therefore more selective. Unfortunately, this method is ineffective with easily ketalized ketones.

Luche has modified the procedure by changing the solvent from methanol to a 1/1.5 ethanol/water mixture.[15] In many cases, improved selectivity is realized as can be seen by comparing the results of competitive studies (Table III). However, the modified procedure has two shortcomings. First, it provides no selectivity with diones, and second, it fails to protect conjugated aldehydes.

Table III.

Competitive acetalization and reduction.

Substrates	% reduction methanol	ethanol/Water
cyclohexane carboxaldehyde	52	22
phenyl propanone	44	93

The latter problem could prove to be advantageous in some circumstances, providing the possibility of selectively reducing conjugated aldehydes in the presence of nonconjugated aldehydes.

Various observations and experiments indicate that hydrates are the protecting species in this system. It is known that conjugated aldehydes are generally not hydrated, and that ketones are hydrated to a lesser extent than nonconjugated aldehydes.[16] These facts correlate very well with the observed selectivity. In addition, acetal or hemiacetal formation can be ruled out as the selectivity is relatively constant when the solvent is changed from ethanol/water to methanol/water or 2-propanol/water.

The following experiment reveals the role of the lanthanide in this reaction. Hexanal and cyclohexanone were dissolved in CD_3OD/D_2O and the NMR spectrum of the mixture was recorded. The absence of an aldehydic proton signal suggested that the aldehyde was entirely hydrated. However, reduction of this mixture with $NaBH_4$ yielded cyclohexanol (100%), hexanol (49%), and hexanal (51%). When the experiment was repeated in the presence of one equivalent of $CeCl_3 \cdot 6H_2O$, hexanal was recovered in 98% yield. Thus, it appears that the lanthanide functions to stabilize the hydrate. Several other ions (H^+, Cu^{+2}, Zn^{+2}, Ba^{+2}, Ti^{+3}, Cr^{+3}, Fe^{+3}) were shown to be inferior to the lanthanides under these conditions.

The Divalent Lanthanides

Although only a few lanthanides have been isolated as divalent salts, their preparation is quite simple. Imamato has prepared CeI_2 by reduction of CeI_3 with potassium, or by treatment of cerium metal with one equivalent of I_2.[17] Samarium and ytterbium diiodides have been isolated by Kagan and coworkers by allowing the metals to react with 1,2-diiodoethane.[10] Divalent europium and thulium salts have also been reported.[18] Kagan and coworkers have found SmI_2 to be the most useful of these salts. A remarkably versatile reagent, SmI_2 is capable of reducing a variety of functional groups as well as forming carbon-carbon bonds. Scheme III gives a summary of the most important reactions of SmI_2.[1]

Scheme III.

Reactions of SmI_2[a]

1) $nC_7H_{15}CHO$	$nC_7H_{15}CH_2OH$	99%[b]
2) $nC_{12}H_{25}I$	$nC_{12}H_{26}$	95%
3) $nC_{12}H_{25}OTs$	$nC_{12}H_{26}$	88%
4) trans-5,6-epoxydecane	trans-5-decene	76%
5) diphenyl sulfoxide	diphenyl sulfide	90%
6) $PhCH_2Br$	$PhCH_2CH_2Ph$	83%[c]
7) $nC_4H_9I + nC_6H_{13}COCH_3$	$nC_6H_{13}C(OH)(CH_3)\text{-}nC_4H_9$	97%
8) $Cl(CH_2)_4OTs + nC_6H_{13}COCH_3$	$nC_6H_{13}C(OH)(CH_3)(CH_2)_4Cl$	62%

[a] Reactions are run in deoxygenated, dry THF either at room temperature or under reflux (required for entries 2 and 3). At least two equivalents of SmI_2 are used and the reaction is quenched after disappearance of Ln^{+2} color.

[b] Solvent was 98% THF and 2% CH_3OH

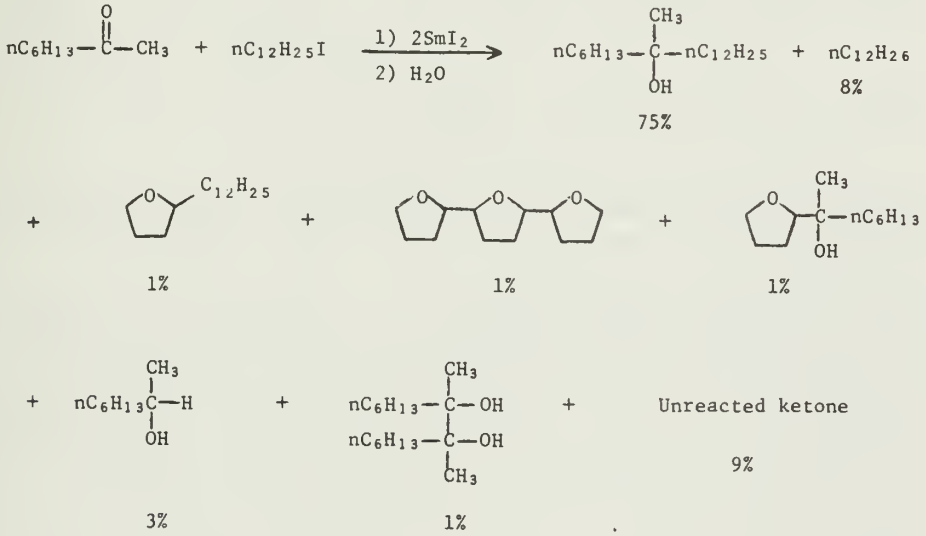
[c] One equivalent SmI_2

Although yields are generally good, in many cases SmI_2 offers no advantages over existing methods,[18,20,21] and is simply another alternative. However, as is true for many lanthanide applications, unusual selectivity makes SmI_2 a useful reagent. For example, aldehyde reduction is easily accomplished with $NaBH_4$, but SmI_2 seems to be one of the best reagents available for the selective reduction of an aldehyde in the presence of a ketone.[22]

The most useful and interesting applications of SmI_2 are the carbon-carbon bond forming reactions, which are formally analogous to Grignard additions (entries 7 and 8, Scheme III). These reactions present several noteworthy features. When an equimolar mixture of ketone and halide is combined with two equivalents of SmI_2, a good yield of tertiary alcohol is obtained. Since the major byproduct of the reaction arises from reduction of the halide, near quantitative yields are realized by increasing the initial proportions of halide and SmI_2. Also, as illustrated by entry 8 Scheme III, selectivity can be observed among alkylating agents. An alkyl chloride will not react with a ketone under these conditions, but a tosylate will. The tosylate reaction apparently proceeds through the corresponding iodide, as addition of a catalytic amount of NaI improves yields. In addition to chlorides, vinyl and aryl halides also fail to react. Perhaps the greatest advantage of this method is that esters react very poorly under the conditions. This permits the selective alkylation of the ketone of a ketoester.

The behavior of allylic, benzylic, and propargylic halides in SmI_2 mediated reactions is interesting. When a ketone is present, it is alkylated smoothly. Where isomers are possible, the predominant product arises from the reaction of unrearranged halide. In the absence of a ketone, a more rapid dimerization occurs (entry 6, Scheme III). In order to explain this phenomenon, and to formulate a mechanism for the reaction in general, several experiments were conducted. First, a complete analysis of the products from the alkylation of 2-octanone with 1-iododecane was performed. Scheme IV gives the results of this study.

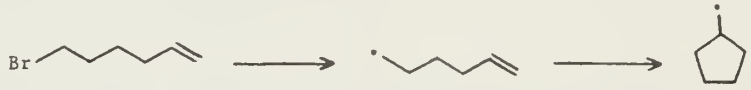
Scheme IV.



The formation of THF derivatives and the pinacolization product suggests that THF radicals and/or anions, as well as ketyl radicals are formed during the reaction. Kagan considered three basic mechanisms which could conceivably rationalize these observations: i) the reaction occurs through formation of an alkyl anion which alkylates the ketone; ii) the product is formed by combination of alkyl and ketyl radicals; iii) electron transfers produce a ketone dianion, which then displaces the halide.

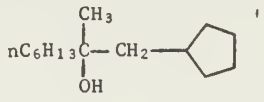
The last mechanism (mechanism iii) was shown not to occur by performing alkylations with optically active alkyl halides. The S_N2 reaction implied in mechanism iii would result in inversion of configuration of the alkyl halide. In practice, when cyclohexanone is alkylated with optically active 2-bromo-octane or ethyl-2-bromopropionate, racemic products are obtained. Thus, the alkyl halide must be converted to a radical or an anion during the reaction.

A classical way to detect radical formation is to add 1-bromo-5-hexene 3 to the reaction mixture. When radicals are present, hexenyl radical 4 is generated, which rapidly cyclizes to methylcyclopentyl radical 5, which can



3 4 5

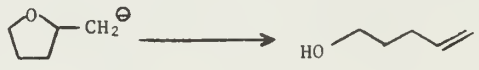
then undergo further reactions. When 3 was employed as the alkylating agent, the major product formed in the reaction with 2-octanone was 6. This clearly



6

indicates the formation of radicals during the reaction. Interestingly, when the reaction was performed in the absence of a ketone, no cyclopentyl derivatives were observed. This suggests that, in the absence of a ketone, the initially formed radical is reduced to the anion faster than cyclization can occur. The anion cannot cyclize.[23]

While the above experiment appears to provide conclusive evidence for the radical mechanism, alkylation of 2-octanone with tetrahydrofurfuryl bromide gives conflicting results. The main product of the reaction is 4-penten-1-ol 8 which arises from rearrangement of tetrahydrofurfuryl anion 7. Since the



7 8

corresponding radical does not rearrange in this manner,[23] this particular reaction apparently proceeds by mechanism i.

It is obviously impossible to choose one of the proposed mechanisms on the basis of these experiments. In fact, since these mechanisms are only limiting cases, the actual mechanism may be some combination of these which is dependent on the substrates and reaction conditions. Whatever the case, Kagan suggests that the alkylation occurs within the coordination sphere of samarium, which is bonded to several THF molecules. When a ketone is present, it is also strongly complexed to samarium and may act as a relay for electron transfer. When allylic or benzylic halides are used, in the absence of ketones, the stabilized radicals or anions formed can escape samarium's coordination sphere and undergo the coupling reactions observed.[24]

Conclusion

Although more work is required on the mechanisms of lanthanide mediated reactions, several groups have already made use of these relatively new reagents.[25] The unusual selectivity, high yields, and high reaction rates have attracted many of these workers. Also, the most useful reagents mentioned herein are not impractical. On the contrary, they are reasonably priced and readily available. With further development, the lanthanide elements should find common usage in organic synthesis.

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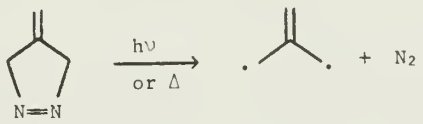
THE PHYSICAL AND CHEMICAL PROPERTIES OF TRIMETHYLENEMETHANES

Reported by Glenn C. Calhoun March 17, 1983

Trimethylenemethane (TMM), 1, and its derivatives are π biradicals.[1] These species have been invoked to explain the thermal rearrangement of Feist's ester and other methylenecyclopropanes.[2] Like other biradicals, TMM remained elusive and generated questions about its nature and chemistry.

The nature of TMM was first discovered when Dowd and his coworkers observed an ESR signal consistent with the triplet TMM.[3] This development led to an interest in the physical and chemical properties of TMM, both as a significant species in its own right and, perhaps, as a model for other biradicals.

TMM has been generated in several ways. The major pathway to 1 has been the thermal or photochemical deazetation of 4-methylene-1-pyrazoline, 2 (Equation 1). Other methods have involved the photolysis of 3-methylenecyclobutanone,[1a] the gas phase pyrolysis of 2-iodomethyl-3-iodopropene,[4] and the irradiation of methylenecyclopropane with ^{60}Co gamma rays.[5]



2 1 (1)

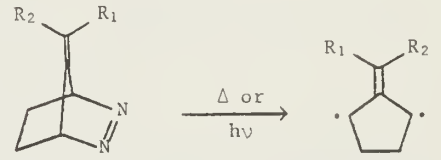
The physical nature of 1 has lent itself well to theoretical orbital energy calculations. All major calculation methods from simple Hückel[1b] to ab initio[6] have generally agreed that the ground state of this biradical is a triplet.

Experimental work has confirmed that the triplet is the ground state. The low temperature photolysis of 2 resulted in an ESR spectrum with four peaks and another strong absorption that was attributed to monoradical impurities.[3] The ESR spectrum was attributed to the triplet based on its fit to a Hamiltonian. The zero-field parameters were found from the spectrum: $D=0.024\ cm^{-1}$ and $E<0.001\ cm^{-1}$. The small values of D and E are indicative of a 1,3-biradical; a small D value indicates a large separation between electrons and the E value indicates D_{3h} symmetry.

Further work by Dowd[1a] led to similar results when the ESR signal was generated by the photolysis of 3-methylenecyclobutanone. In this spectrum, a $\Delta m=2$ absorption is seen, a characteristic indication of a triplet species. The ESR spectrum of a single crystal of 3-methylenecyclobutanone was a 7 line pattern with binomial relative heights, reflecting the interaction of the electrons with six equivalent hydrogens.

The postulation of the triplet as the ground state is consistent with the generation of a straight line from a Curie law plot of I, the intensity of the signal, versus 1/T.[7] This argument assumes that the energy difference between the singlet and the triplet is greater than RT.

Berson and his coworkers have also observed triplet ESR signals for a series of TMM derivatives, 3a-f.[8,9] The irradiation of 4f at low temperatures resulted in a strong six line pattern. The measured zero-field parameters were similar to those observed by Dowd: D=0.027 cm^{-1} and E = 0.0023 cm^{-1}. The other derivatives gave similar signals. In addition, 3a, c, d, and f all show $\Delta m=2$ peaks. Curie law plots resulted in straight lines for 3a-f.



4 a $R_1=R_2=H$ d $R_1=R_2=Ph$ 3 a-f
b $R_1=H$, $R_2=Ph$ e $R_1=R_2=OMe$
c $R_1=H$, $R_2=Cl$ f $R_1=R_2=Me$

The chemistry of these 1,3-biradicals has been the major interest of experimental chemists since the first observation of the ground state triplet of 1. Early work in this area proved to be difficult because of the tendency of 2 to rearrange to 4-methylpyrazole in the presence of light or water, and the tendency of 1 to close to methylenecyclopropane, even in the presence of olefins which should be able to trap the biradical. The closure to methylenecyclopropane can be most reasonably explained as the reaction of a singlet TMM, but the inability to trap this species left its existence without substantial proof. The work of Berson, using primarily 7-isopropylidene-2,3-diazanorbornene, 4f, to generate 2-isopropylidenecyclopenta-1,3-diyl, 3f, has avoided the problems stated above, and provided much insight into the chemistry of this TMM derivative.

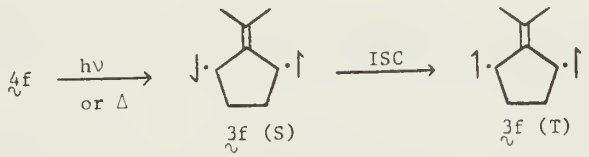
It is generally believed that dimerization is a characteristic reaction of the triplet biradical. The pyrolysis or photolysis of 4f in the absence of trapping agents led to a high yield of dimers of 3f.[8,10] In principle, there are four possible structures for the dimers with two stereoisomeric forms possible for each. Berson reports the separation and characterization of only six of the possible dimeric products.[10] It was found that the ratio of products was the same for both methods of deazetation. This is necessary but insufficient evidence for the postulation of a common intermediate for the photochemical and thermochemical processes.

The nature and kinetics of the triplet reaction have been probed by CIDNP[8] and ESR.[11] Pyrolysis of 4f in a fluid medium led to a strong CIDNP emission. An extension of the radical pair theory by Closs[12] showed that at least one of the interacting intermediates must be a triplet. This limits the mechanism of dimerization to a singlet + triplet or a triplet + triplet reaction. ESR kinetics have pointed toward a triplet + triplet reaction.[11] The decay of the triplet ESR signal was second order in [triplet] with a rate constant of $(2.2 \pm 1.3) \times 10^3$ M^{-1} s^{-1}. This does not rule out the singlet + triplet mechanism if the singlet and the triplet are in rapid equilibrium. However, it has been shown that the rate constant for the singlet + triplet addition would exceed the bimolecular difussion-controlled rate constant from the Debye-Stokes-Einstein model if the singlet-triplet gap was higher than 600 cal/mole. A ΔE value of 600 cal/mole is a very

conservative estimate from the Curie law plots and is believed to be too low according to the experiments described below. Thus, Berson favors the triplet + triplet mechanism for the dimerization of $\underset{\sim}{3}$f.

Although the triplet has been established as the ground state of TMM and its derivatives, the mechanism leading to the triplet ground state has been difficult to determine. In early experiments by Crawford and Cameron,[13] a small value of $\Delta S^{\neq}$ was found by an Arrhenius plot from the gas phase pyrolysis of $\underset{\sim}{2}$. This value is much smaller than the $\Delta S^{\neq}$ value for the pyrolysis of 1-pyrazoline, and can suggest a spin forbidden path directly from the reactant to the triplet ground state. This pathway makes it difficult to explain the production of methylenecyclopropane, which is generally believed to come from the singlet biradical. Experimental work by Berson has resulted in the separation of two species that he believes to be the singlet and triplet forms of $\underset{\sim}{3}$f and the proposition of a cascade mechanism (Scheme I) to explain the behavior of the intermediates in the thermal and photochemistry of $\underset{\sim}{4}$f.[10,14,15]

Scheme I



One of the ideas inherent in Berson's design of his TMM derivatives was the hope that ring closure of the biradicals would be either thermodynamically or kinetically unfavorable under the reaction conditions. If this were true, the amount of cycloaddition product with olefin might be increased over that seen for the parent TMM system. Pyrolysis of degassed solutions of $\underset{\sim}{4}$f have given cycloadducts in good yields when conjugated olefins are used.[16,17] Olefins, such as fumaronitrile, can give up to 95% of the 1:1 cycloadducts.[17b] Unconjugated olefins and acetylenes give poor yields of cycloaddition products. This ability to recover high yields of cycloaddition products has provided the major evidence in favor of the proposed cascade mechanism.

The cycloaddition of the olefin and the 1,3-biradical can result in either fused ring products or bridged products with several possibilities for stereochemistry (Scheme II). The pyrolysis of $\underset{\sim}{4}$f in the presence of an olefin showed first order kinetics in $\underset{\sim}{4}$f, zero order in olefin, and a product ratio dependent on olefin concentration.[10,14] When $\underset{\sim}{4}$f was pyrolyzed in the presence of varying concentrations of dimethyl maleate (DMM) or dimethyl fumarate (DMFum), a change in the regio- and stereochemistry of the products was observed with changing olefin concentration. At high concentrations of olefin, the products exhibited high regioselectivity for the fused ring adducts. These products were also stereospecific with predominently cis stereochemistry from DMM and trans from DMFum. At lower concentrations of olefin, randomization of regiochemistry and loss of stereospecificity is seen (Table I, Table II).

Scheme II

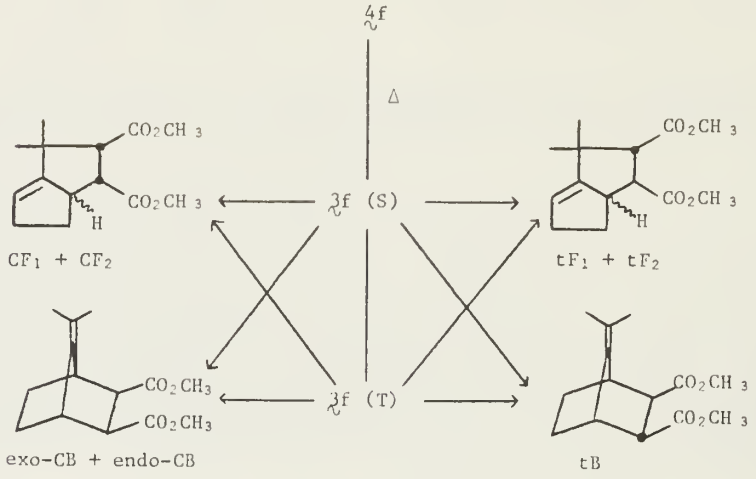


Table I. Composition of Product Mixture from Pyrolysis of 4f in the Presence of DMM in CH_3CN at 60°C.[10]

	% products					
[DMM] M	tF1	tB2	tF2+ CF1	CF2	CB	total adducts
6.6	9.9	22.7	30.0	34.7	2.9	95
3.3	11.3	25.1	29.8	32.0	1.8	95
1.32	16.9	36.7	22.3	20.2	4.0	93
0.66	18.8	43.1	19.4	14.1	4.2	86
0.33	21.5	49.1	15.7	7.9	6.0	59
0.13	22.4	51.1	14.6	6.3	5.5	38
0.066	23.2	42.0	14.1	5.5	5.4	24
0.033	24.2	51.2	12.9	5.4	6.1	12

[a]The balance of total adduct is dimer.

Table II. Composition of Product Mixture from Pyrolysis of 4f in the Presence of DMFum in CH_3CN at 60°C.[10]

	% products					
[DMFum] M	tF1	tF2	tB	CF2	CB	total adducts
0.515	51.4	38.1	9.9	a	0.6	100
0.204	48.7	32.5	17.6	a	1.2	100
0.0725	42.8	23.0	30.3	a	3.9	a
0.035	39.2	18.0	36.9	0.05	5.9	a
0.017	37.9	14.0	41.2	0.4	6.5	98.5
0.007	36.8	11.6	44.5	0.12	7.0	95.6

[a]Not determined

[b]The balance of total adduct is dimer.

This change in products can be explained by the intervention of two or more intermediates. Berson believes that this dilution effect on the products can be consistently explained by the reactions of $\underset{\sim}{3}$f (S) and $\underset{\sim}{3}$f (T). In the cascade mechanism, the intermediate trapped at high olefin concentration should be $\underset{\sim}{3}$f (S). The stereospecificity of the singlet biradical is reminiscent of the chemistry of singlet carbenes.[18] The singlet should be capable of adding in a concerted fashion which explains the stereospecificity of the cycloaddition products. At lower concentrations, the loss of stereochemical integrity and the randomization of regiochemistry can be explained by an intersystem crossing from $\underset{\sim}{3}$f (S) to $\underset{\sim}{3}$f (T). The triplet would add to the olefin in a stepwise manner which allows for the observed product composition changes. Mathematical treatment of the fraction of product as a weighted average of that product from two intermediates and the mutual dependence of the yields of various products argues against the involvement of more than two intermediates.

The assignment of $\underset{\sim}{3}$f (S) and $\underset{\sim}{3}$f (T) as intermediates has been tested by several experiments. The irradiation of $\underset{\sim}{4}$f in the presence of DMFum and xanthone, a triplet sensitizer, produced a ratio of fused to bridged cycloaddition products that was the same as that found by extrapolation of the dilution experiment data to zero concentration.[15] In a separate experiment, the yields of cycloadducts were determined in the presence of O_2, a known triplet scavenger, at 250 torr.[10] For DMM a reduction in triplet products was seen at dilute olefin concentrations while the product composition remained constant over a wide range of concentrations when DMFum was used. The product compositions in this experiment were similar to those seen at high olefin concentration. These experiments are consistent with the assignment of $\underset{\sim}{3}$f (S) and $\underset{\sim}{3}$f (T) as the intermediates and also provide product compositions characteristic of "pure" singlet and "pure" triplet reactions. These characteristic compositions have been used to rank the reactivity of olefins toward $\underset{\sim}{3}$f (S) and $\underset{\sim}{3}$f (T).[17]

The regiospecificity of the singlet can be explained in two ways.[19] The first explanation invokes a bisected singlet as the important intermediate. In this view, the fused ring would be set up to form quickly, while the bridged product would form slowly because of the need to twist the bisected orbital back into the plane in order to form the final product.

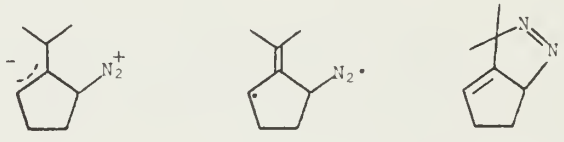
The second explanation employs a frontier molecular orbital argument. In both possible cases, either combination of the HOMO of $\underset{\sim}{3}$f (S) and the LUMO of the olefin or the LUMO of $\underset{\sim}{3}$f (S) and the HOMO of the olefin leads to the prediction that the fused ring would be favored.

In order to discern between these two alternatives, Berson reacted $\underset{\sim}{3}$f (S) with a diene.[19] The change to a diene allows for 1,2-addition and 1,4-addition. In the bisected biradical explanation, the fused ring product should be favored in both the 1,2- and 1,4-addition. On the other hand, the frontier molecular orbital argument predicts a switch in the allowed products. The 1,2-addition should give predominantly fused product and the 1,4-addition should give bridged products.

Cyclopentadiene was chosen for its favorable s-cis configuration but led to problems due to its oxidation at high O_2 pressures and its dimerization during analysis by gas chromatography. The thermal generation of 3f in the presence of high concentrations of cyclopentadiene gave high yields of fused 1,2-products and bridged 1,4-products. Photolysis of 4f at high concentrations of cyclopentadiene gave a 95% yield of the expected products. The product distribution was about the same for both methods. Cyclopentadiene at low concentrations gave randomization of regiochemistry in the products similar to the behavior of monoolefins.

These results tend to support the planar 3f (S) over the bisected species, although the two may both be involved in the singlet reaction. This rationalization of the regiochemistry is somewhat questionable because it disregards the differences in the molecular orbital properties of biradicals and ground state molecules. It also assumes that the symmetric non-bonding orbital is lower in energy than the antisymmetric non-bonding orbital in the biradical.

The possibilities of the existence of other intermediates besides 3f (S) have been explored. One possible intermediate could result from the stepwise loss of nitrogen. This could result in a biradical 5 or its zwitterionic form, 6. The zwitterionic form can be excluded from consideration because the behavior of the intermediate does not change with changing solvent polarity.[20] Early experiments by Berson[21] seem to speak against the stepwise loss of nitrogen. The pyrolysis of endo-5,6-dideuterio-7-isopropylidene-2,3-diazonorbornene in the presence of DMFum led to a 50% yield of both the endo- and exo-dideuterio cycloaddition products. Berson believes that this result is difficult to assign to the stepwise loss of nitrogen and is more consistent with the symmetrical nitrogen-free intermediate. However, later experiments with 4f and its fused ring isomer, 2,2-dimethyl-3,4-diazabicyclo[3.3.0]octa-3,8-diene, 7, show that the pyrolysis of 4f leads to a rearrangement to 7. The reaction of 4f is followed by NMR using a europium shift reagent to differentiate between 4f and 7. The ratio of 4f/7 changes from $\geq$20 to 2.5 after 8.5 hours of reaction. Since the pyrolysis of 7 was shown to be faster than that of 4f in separate experiments, this result must be due to the rearrangement of 4f to 7. This speaks in favor of an intermediate like 5.



6 5 7

This experiment casts some doubts on the assumption that the thermochemical and photochemical pathways have the same intermediates, since the photochemistry of 4f does not show rearrangement to 7. Nevertheless, no nitrogen containing addition products have been found and the same product mixtures have been seen from the pyrolysis or photolysis of 4f and the pyrolysis of 7, which does not rearrange to 4f.

Two strained hydrocarbon systems were also investigated as possible intermediates: 2,6,6-trimethylbicyclo[3.1.0]hex-1-ene, 8, and 5-isopropylidenebicyclo[2.1.0]pentane, 9.



8 8a 9 10

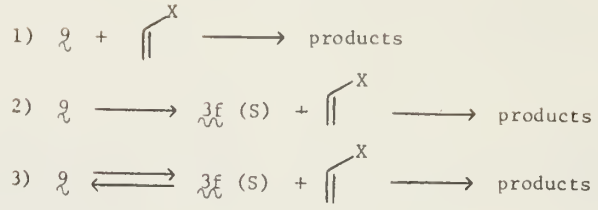
The chemistry of 8 was quite different from that seen from the intermediates in the deazetation of 4f.[22,23] Generation of 8 at -78°C led to mainly a [π + π] dimer. At 0°C, a small amount of [π + π] dimer is found, and dimers of 3f are also found. Intermolecular capture of 8 with olefins proved to be difficult because in situ generation of the bicyclic hydrocarbon via a vinyl carbenoid species, 8a, was incompatible with most olefins. The reaction of a derivative of 8 with excess 1,3-diphenylisobenzofuran gave a 5% yield of a Diels-Alder product, 10, with the bicyclic structure of 8 intact. These results speak against 8 as an intermediate in the deazetation of 4f, although there is evidence that TMM derivatives can be generated by bond cleavage of 8.[23]

Strained hydrocarbons, such as 9, hold much more promise as intermediates. The synthesis and thermochemistry of 9 has recently been reported by Berson.[24] Nearly quantitative yield of 9 was obtained by the photolysis of 4f at -78°C. Solutions of 9 are surprisingly stable at these temperatures; the half-life of 9 was 3 hours at -53°C by NMR spectroscopy.

Several experiments have been carried out to determine the thermochemistry of 9.[24,25] Dimers of 3f were obtained in the same proportions that were seen in the photolysis or pyrolysis of 4f when solutions of 9 were allowed to warm to -53°C. The kinetics are cleanly first order in 9, with E_a values of 13.6 and 13.3 kcal./mole and log A (A is s^{-1}) values of 9.6 and 9.2. In the presence of an excess of acrylonitrile, a relatively poor trapping agent, at -78°C, the photolysis of 4f gave primarily 9. On warming the mixture, cycloaddition products reminiscent of those from the pyrolysis of 4f are found. Kinetic investigation of the mechanism considered three main cases (Scheme III).[25] Cases one and two represent the possibilities of second and first order kinetics, respectively, whereas case three allows for intermediate behavior with extreme behavior when the capture or ring opening step is the rate determining step. Double reciprocal plots of $1/k_{obs}$ versus 1/[olefin] gave a non-zero slope and a non-zero intercept under pseudo-first order conditions when acrylonitrile was the olefin. This result speaks against cases one and two. Further experiments with maleic anhydride, an extremely good trapping agent, produced a straight line with a slope of zero and the same intercept as in the experiment with acrylonitrile, a result consistent with case 3.

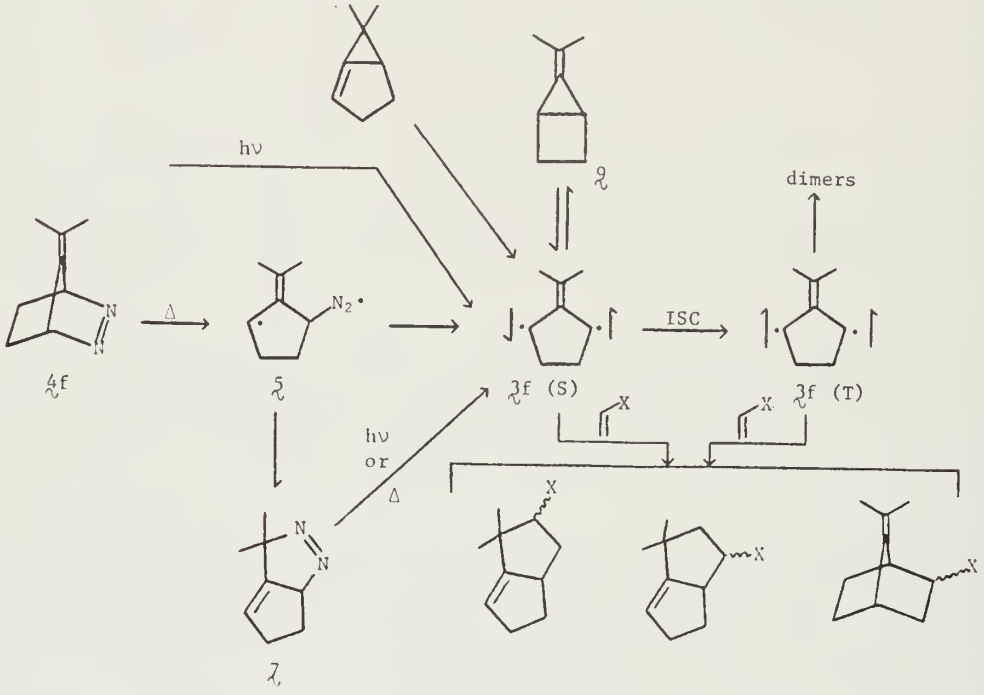
The results of the cycloaddition reactions rule out 9 as the sole intermediate responsible for the products formed from the photolysis or pyrolysis of 4f, although the product forming intermediate can be generated from 9. These results, in Berson's opinion, leave 3f (S) as the only plausible intermediate to explain the cycloaddition chemistry.

Scheme III



A summary of the chemistry of 4f and the resulting TMM biradicals is given in Scheme IV.

Scheme IV



Although Berson's contribution has been the greatest, other workers' findings back Berson's conclusions. Gajewski,[26] and Skell[4] have both identified methylenecyclopropane, a singlet product, from the generation of 1. The experiments of Gajewski in the vapor phase photolysis of 2 are consistent with Berson's proposed cascade mechanism. Direct photolysis of 2 in the vapor pahse with 32 torr of cyclohexane gave only a 10% reaction to methylenecyclopropane. However, if cyclohexane was replaced by benzene, the percent yield went up to 60. A 6.2:1 ratio of methylenecyclopropane to TMM dimer was found in the latter case. Introduction of 11 torr of O_2 completely suppressed dimer formation and gave a 34% yield of methylenecyclopropane.

Dowd has recently reported experiments to measure the singlet-triplet energy gap of 1 and the activation energy for ring closure.[5] Using Benson's additivity rules, an activation energy for ring closure of 25.3 kcal./mole was calculated, but this is not in accord with the disappearance of the ESR signal at -140°C. The activation energy for ring closure was determined to be 7 ± 1 kcal/mole. This value is a bit small when compared with recent theory (15.2 kcal/mole)[27] and Berson's estimates from his system (13.6 kcal/mole).[25]

The extensive work in the field of TMM and its derivatives has provided much insight into the physical and chemical properties of these observable biradicals. ESR spectroscopy has established the triplet TMM as the ground state of many of these biradicals, and the work by Berson has provided a consistent mechanism to explain the chemistry of these species.

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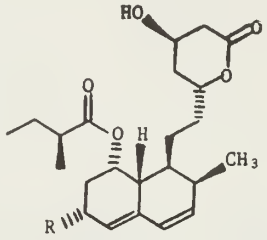
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SYNTHETIC APPROACHES TO COMPACTIN, MEVINOLIN AND THEIR ANALOGUES

Reported by Han-Young Kang March 21, 1983

Introduction

Recently an important new class of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors was discovered. The first member of this family, compactin (1a) also known as ML-236B, is a fungal metabolite isolated virtually simultaneously in 1976 by Brown et al (Beecham Pharmaceuticals)[1] and Endo et al (Sankyo Co.)[2] from Penicillium brevicompactum and Penicillium citrinum respectively. Another hypocholesterolemic metabolite mevinolin (1b)[3] (or monacolin K[4]) produced by Aspergillus terreus and Monasus ruber respectively, has more recently been isolated.



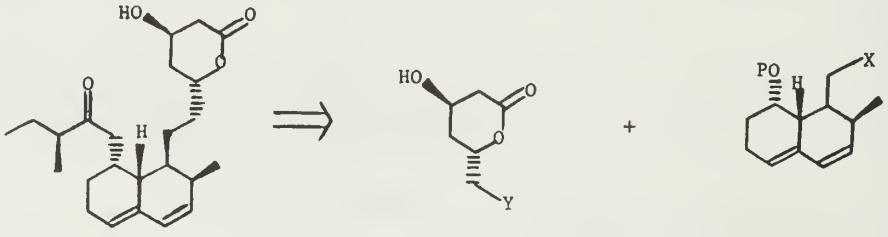
1a R = H; compactin (ML-2368)
1b R = CH_3; mevinolin (Monacolin K)

Both compounds are potent competitive inhibitors of 3-hydroxy-3-methylglutaryl -CoA (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol biosynthesis.

Several fungal metabolites have been shown to be potent inhibitors of HMG-CoA reductase activity. The ML series, including ML-236B (compactin) is one of the most studied groups of fungal metabolites showing this activity. Of great significance is the observation that ML-236B effectively reduces plasma cholesterol levels in a number of species including dogs, monkeys and humans.[5] It has been known that mevinolin is slightly more active than compactin in inhibiting HMG-CoA reductase activity.[6]

Synthetic Approaches

In the retrosynthetic analysis, compactin (and its derivatives) can be divided into two parts, the lactone portion (4) and the hexahydronaphthalene portion (5).



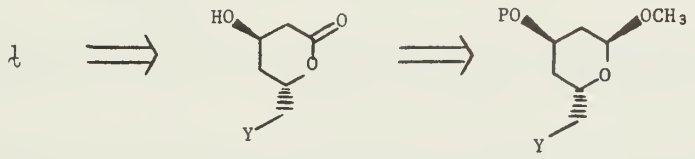
1a 4 5

In this abstract synthetic approaches to compactin (and mevinolin and their analogues) will be discussed first based on this synthetic analysis followed by other synthetic approaches.

Synthetic Approaches to Tetrahydropyran Moiety (Lactone Portion)

The first attempt to synthesize analogues of compactin was made by Soto et al.[7] Several mevalonolactone analogues (the lacton portion is similar to that of mevalonolactone) were made in order to investigate the structure-activity relationship.

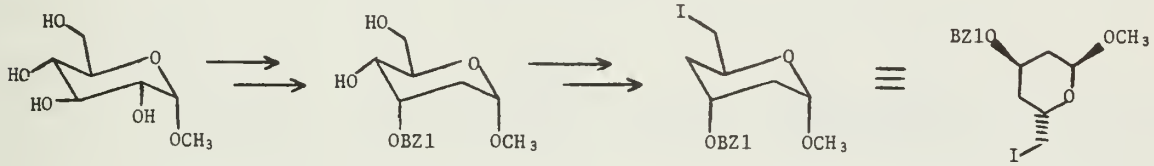
Several approaches to synthesize the key intermediate for the lactone portion which possesses the required absolute stereochemistry (Structure 6) have appeared.



4 6

Prugh and Deana[8] proposed that the lactone fragment of these potent HMG-CoA reductase inhibitors could be synthesized from D-glucose, a readily available starting material which already has the requisite absolute stereochemistry. The synthetic sequence is outlined in Scheme I. Some model compounds were prepared using this intermediate 7.

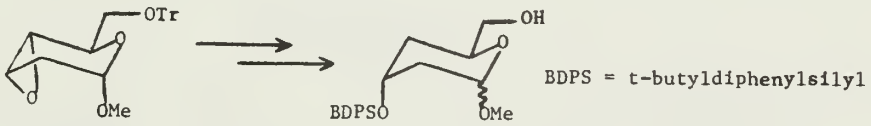
Scheme I.



7

Another approach to synthesize a similar intermediate and its elaboration into some mevinate analogues was reported by Yang and Falck.[9] The known epoxytrityl ether 8[10] was used as a starting material (Scheme II).

Scheme II.

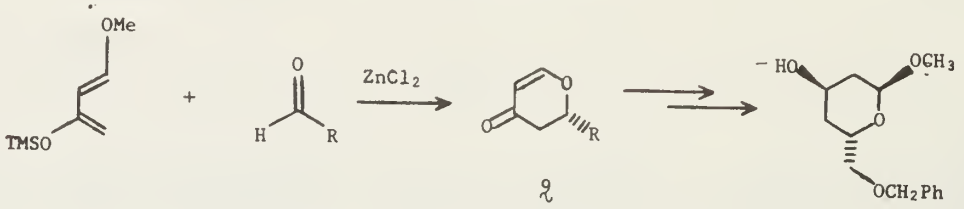


8

Danishefsky and coworkers[11] devised an interesting approach to compounds such as 6. The retrosynthetic analysis emphasized precursor 9 which might be derived from the cycloaddition between diene and heterodienophile (Scheme III). Diels-Alder reaction of conjugated dienes and carbonyl groups have been previously reported especially in the case of reactive carbonyl groups.[12] High pressure has also been used to catalyze the reaction.[13] The promotion of the

cycloaddition by a Lewis acid such as zinc chloride, boron trifluoride or alkoxyaluminum dichloride has been reported by Danishefsky et al and Scheeren et al.[14] Danishefsky's approach to 6 using a Diels-Alder reaction with acid catalyst is shown in Scheme III.

Scheme III.



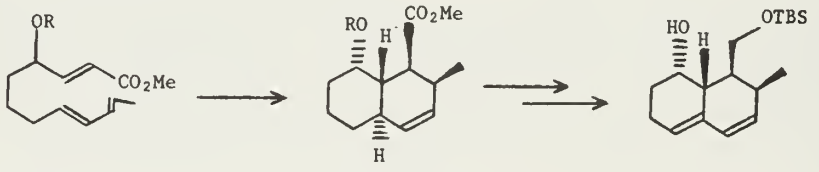
9

Synthetic Approaches to the Hexahydronaphthalene Moiety

From the structure of the bottom part of compactin and mevinolin, it is obvious that the synthetic approach should involve the effective introduction of several chiral centers in the molecule.

Intramolecular cycloaddition might be a useful approach to this kind of system.[15] Funk and Zeller[16] realized this and tried to synthesis the hexahydronaphthalene portion of compactin via an intramolecular Diels-Alder reaction. From the retrosynthetic analysis they expected that intramolecular cycloaddition of dodecatrienoate 10 would be an efficient pathway to the hexahydronaphthalene moiety (Scheme IV). Funk and Zeller found that in the cycloaddition reaction the relative amount of the desired cycloadduct 12 and 13 could be significantly increased by addition of $EtAlCl_2$. Conversion of cycloadduct 13 to 14 was also achieved.

Scheme IV.



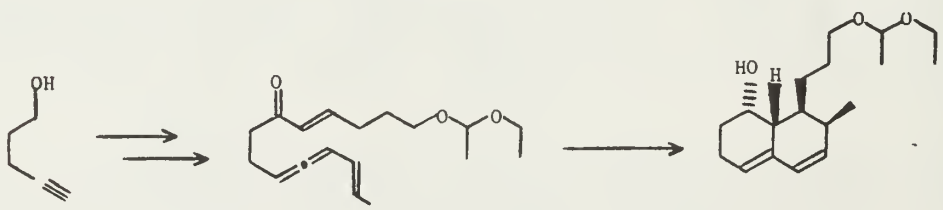
10 R = H
11 R = TBS

12 R = H
13 R = TBS

14

Another approach to the hexahydronaphthalene moiety using an intramolecular Diels-Alder reaction was discovered by Deutsch and Snider.[17] The key step in this approach involves the use of vinylallenes as dienes in the Diels-Alder reaction taking advantage of the rigidity of allene[18] (Scheme V).

Scheme V.

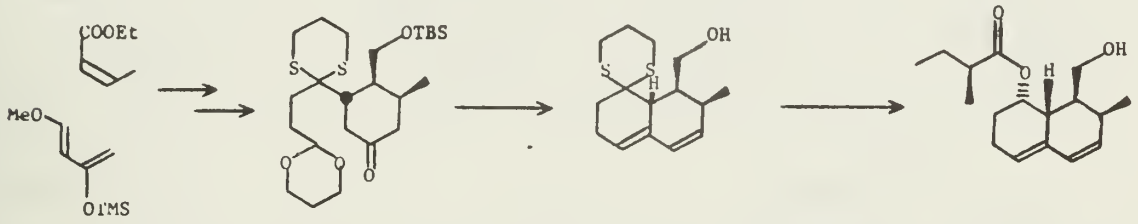


15 16 17

The synthesis of vinylallene 16 was accomplished from 4-pentyn-1-ol (15) by several steps including coupling with crotyl bromide, and, after oxidation, reaction with an acetylide from the ethoxy ether of 4-pentyn-1-ol and isomerization. An intramolecular Diels-Alder reaction afforded the desired cycloadduct efficiently, after which L-Selectride reduction gave 17.

Heathcock et al[19] have also reported the synthesis of the hexalin moiety using a cyclohexene annelation process which they developed previously.[20]

Scheme VI.



18 19 20

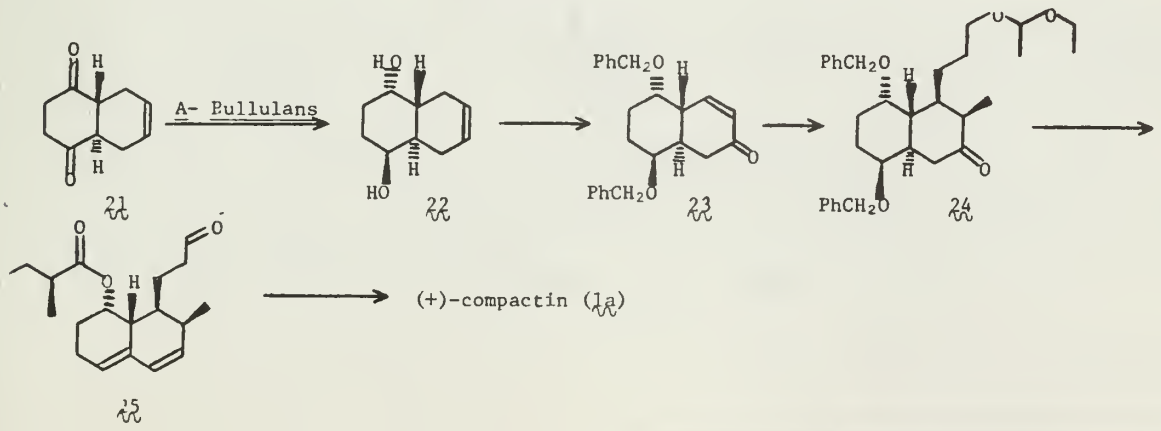
The synthesis (Scheme VI) started with the cycloaddition between Danishefsky's diene and ethyl crotonate. After several steps, 18 was obtained, subjected to an annelation and then finally converted to 20 which can be utilized for the preparation of analogues of compactin.

Total Synthesis of (+)-Compactin

The first total synthesis of naturally occurring (+)-compactin was reported by Sih and coworkers.[21] Central to their synthetic plan was the development of the viable route to 24 (Scheme VII). It was projected that key intermediate 24 be prepared by the conjugate addition between cuprate and enone 23 and trapping of the enolate with a suitable electrophile.

Starting with the readily available trans-dione 21, trans-diol(-)-22 was produced in 33% yield by microbiological conversion (Aureobasidium pullulans). Conversion to enone 23 was accomplished by the reaction with phenyl selenylbromide followed by oxidation. Reaction of enone 23 with the mixed cuprate followed by quenching with formaldehyde, mesylation, elimination, and finally hydrogenation yielded the desired 24 as the major product. After conversion to aldehyde 25 by several steps involving tosyl hydrazine treatment (followed by LDA) and reaction with excess methylbutyric anhydride and selective hydrolysis the lactone portion was incorporated by the reaction with the dianion of methyl acetoacetate. Finally lactonization and separation led to completion of the total synthesis of (+)-compaction.

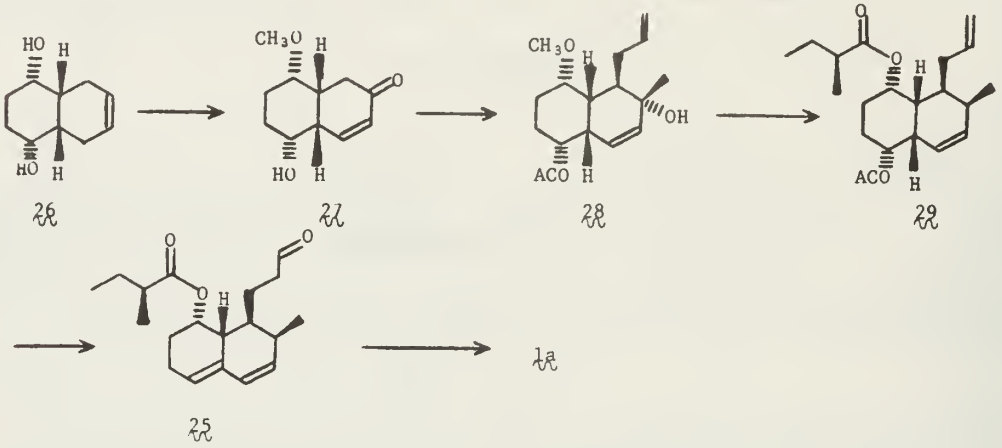
Scheme VII.



21 22 23 24 25

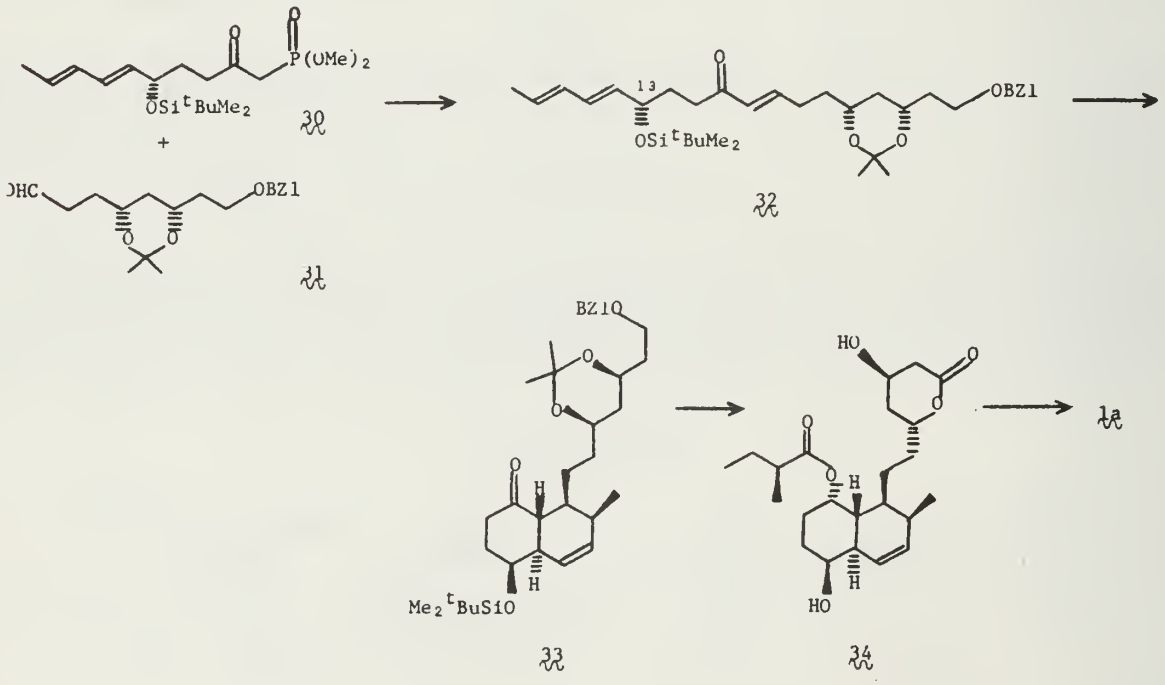
Another synthetic approach (Scheme VIII) starting from cis-diol 26 which originated from butadiene and p-benzoquinone was reported by Girotra and Wendler.[22] A more or less similar approach to that of the first total synthesis by Sih et al was used.

Scheme VIII.



After conversion of cis-diol 26 to enone 27 Allylation and methylation with proper protection and deprotection afforded alcohol 28. Oxidation and tosylhydrazine treatment followed by reduction with catechol borane, cleavage of the methyl ether, and acylation resulted in 29. Hydroboration, selective hydrolysis after protection, and finally elimination yielded aldehyde 25. The transformations after this stage were almost the same as the procedure by Sih et al.

Scheme IX.



A third approach to synthesize (+)-compactin via intramolecular Diels-Alder Reaction was reported by Hirama and Uei[23] (Scheme IX). The intramolecular Diels-Alder reaction of trienone 32 could be a viable approach to a trans-octalone system such as 33 and for the concomitant asymmetric induction of four asymmetric centers. From the preliminary study they noticed that S configuration at C13 is required for the entry to compactin. The two segments 30 and 31 were prepared in optically active forms. After coupling of these segments, trienone 32 was subjected to cyclization in refluxing chlorobenzene which led to the desired 33 (28%; along with two other isomers). K-Selectride reduction introduced axial alcohol and esterification, debenzylation and finally oxidation produced the ester which, after diazomethane treatment, was further converted into 34 by exposure to HF-CH_3CN. Then 34 was subjected to selective protection, dehydration and deprotection which resulted in the completion of another total synthesis of (+)-compactin.

Other Studies

Synthetic sequences for modifying the side-chain ester and lactone moieties of mevinolin have been also published.[24,25] Elaboration of the side chain ether analogues of mevinolin as well as the mevalonate analogues have been performed. Also, homologation of the lactone ring was worked out.

Summary

Compactin (and mevinolin) make a challenging synthetic target because of the presence of several asymmetric centers, a high degree of functionalization, and the highly sensitive lactone portion which is essential for biological activity. In two years, since the first total synthesis was reported, extensive synthetic studies have resulted in the synthesis of the lactone moiety, hexalin nucleus, and their simpler analogues. This class of molecules is attracting continuing attention in synthetic studies[26] as well as biological evaluation.

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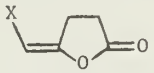
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SYNTHESIS AND STUDY OF HALOENOL LACTONES AS ENZYME-ACTIVATED IRREVERSIBLE INHIBITORS OF SERINE PROTEASES

Reported by Michael J. Sofia March 24, 1983

The development of enzyme-activated irreversible inhibitors (suicide inactivators) has attracted significant attention in recent years.[1] Utilizing its catalytic machinery, the target enzyme plays the essential role of unmasking a latent reactive functional group contained in the suicide inactivator molecule, revealing a reactive electrophilic species that may alkylate the enzyme. The potential for generating this reactive species exclusively within the active site of the enzyme imparts, in principle, a much higher degree of selectivity to these inhibitors than that exhibited by conventional active-site-directed irreversible inhibitors. Thus suicide inactivators have found utility in in vitro enzyme studies and in vivo biochemical investigations,[2] and several have shown promise as clinically useful drugs.[3]

Rando[4] proposed that a haloenol lactone such as 1 would, on acyl transfer to the active site hydroxyl group of a serine protease, release an α-haloketone that could alkylate accessible nucleophilic residues. Thus, lactone 1 might

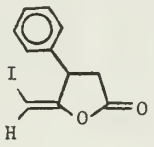


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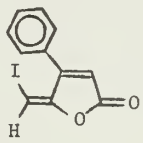
be a prototype for a series of effective enzyme activated protease inactivators more versatile than existing protease suicide substrates.[5]

Rando's proposal prompted the development of several aryl-substituted 5- and 6- membered ring haloenol lactones.[6,7] Experimental results with these haloenol lactones supported the proposed theory of enzyme-activated irreversible inactivators.[8] In fact, the α-naphthyl-substituted lactones have proved to be extremely efficient chymotrypsin inactivators.[8]

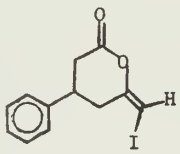
In developing these haloenol lactones further as enzyme-activated irreversible inactivators of serine proteases, several aryl substituted lactones 2, 3, and 4 were synthesized to study the effect of lactone substitution pattern with regard to their binding and inactivating potential.



2

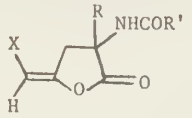


3



4

We also believed that it might be possible to attain greater selectivity towards a specific protease by preparing analogs of oligopeptides known to be highly selective substrates for these proteases.[9] These oligopeptide inactivators would contain an α-amino haloenol lactone in place of the scissile amino acid unit and would have the remaining peptide chain appended to the α-amino group on the lactone. Thus haloenol lactone analogs 5 were prepared to study their binding and inactivating ability toward proteases.[10]



5

When comparing their inactivation of α-chymotrypsin, the pyranones (3 and 4 substituted) were found to be superior to the corresponding furanones. Also, the 3-amino lactone system 5 showed improved inactivation in the order R = H< benzyl<phenyl, but they showed no improvement over the earlier lactones.

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RECENT AND DIVERSE REGIOSPECIFIC APPROACHES TO (±) DAUNOMYCINONE

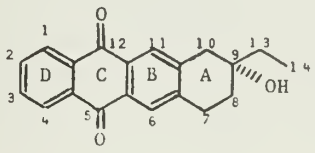
Reported by Jeff Zablocki April 4, 1983

Introduction

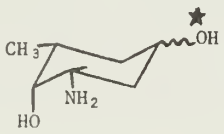
Daunomycin (1a, daunorubicin) is a member of a polycyclic class of compounds called anthracyclines (1*, base structure). Daunomycin was first discovered in the mycelial mass of Streptomyces peucetius in the laboratories of Farmitalia in the early 1960's.[1] Daunomycin was found to have potent cytotoxic activity in cell cultures and to inhibit the multiplication of viruses. Although highly toxic, daunomycin was used clinically in the treatment of acute leukemias in the mid-1960's. In 1969, adriamycin (2a, doxorubian) was shown to be less toxic than daunomycin and displayed activity against a much broader range of tumors, and replaced daunomycin in clinical use.[2] The dose related cardiotoxic effects[3] of daunomycin and adriamycin presented a challenge for synthetic chemists to prepare analogs of compounds 1-3 which have an improved therapeutic index. In working toward the synthesis of analogs of 1-3 there has been a great deal of work done on the synthesis of daunomycinone 1b itself (the aglycone of daunomycin).[4]

The structure of daunomycinone 1b offers three principal synthetic challenges: the generation of the tetracyclic skeleton, generation of the A-ring functionality, and achievement of the required regiochemical juxtaposition of the substituents in the A- and D- rings. This review covers recent and diverse regiochemical syntheses of (±) daunomycinone. Recently, there have been advances made in the area of analogs of compounds 1-3, in particular, 4-demethoxydaunomycinone, 11-deoxydaunomycinone, and alklavinone derivatives.[5] The broad area of analogs of daunomycinone is beyond the scope of this review. References are supplied as a starting point for those interested in analogs of daunomycinone.[5]

Figure 1.



Structure 1 *



L-daunosamine
★ position of attachment

	Position of phenolic groups	Ring-A substituents at positions 7	10	Others
(±) Daunomycinone 1b	6,11;4-OCH_3	OH(S)	H	13-OXO
(±) Adriamycinone 2b	6,11;4-OCH_3	OH(S)	H	13-OXO,14-OH
(±) Carminomycinone 3b	4,6,11	OH(S)	H	13-OXO
(±) Alklavinone 4b	4,6	OH(S)	CO_2CH_3	------

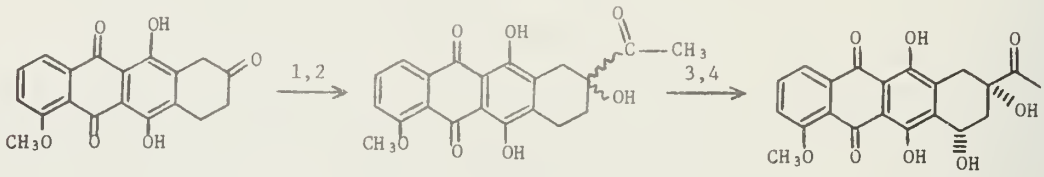
a = mycin series L-daunosamine at 7-position
b = mycinone series -OH at 7-position

Interconversions among anthracyclinones 1-3 have been developed. Daunomycinone 1b can be converted to adriamycinone 2b in two steps in 87% yield via enol bromination at C-14 and subsequent hydroxide displacement.[6] The C-4

methoxy of daunomycinone 1b can be demethylated by $AlCl_3$(~100%)[7] to carminomycinone 3b, and carminomycinone can be methylated to daunomycinone (CH_2N_2,45%).

A common intermediate in daunomycinone total synthesis is tetracyclic ketone 5 which can be converted to (±) daunomycinone in four steps (10% overall yield, Scheme 1). The hydrolysis is done on moist silica gel which gives a 5:2:1 ratio of (±) 7-epidaunomycinone, (±) daunomycinone, and recovered 7-deoxy compound. The (±) 7-epidaunomycinone can be epimerized in trifluoroacetic acid (25°C, 2h) to give after silica gel chromatography (±) daunomycinone 1b (76%).[7]

Scheme 1.



5 6 1b

Conditions 1) HC≡CMgBr (52%) 2) mercuric oxide, H_2SO_4(3m), 70°, 3h (40%) 3) Br_2, CCl_4, sunlamp (position 7) 4) hydrolysis-moist silica gel (50% overall for steps 3 & 4).

The synthetic routes to daunomycinone rely heavily on three major reaction classes: Friedel-Crafts alkylations or acylations, Diels-Alder reactions, and nucleophilic condensations. The various routes are discussed under these headings.

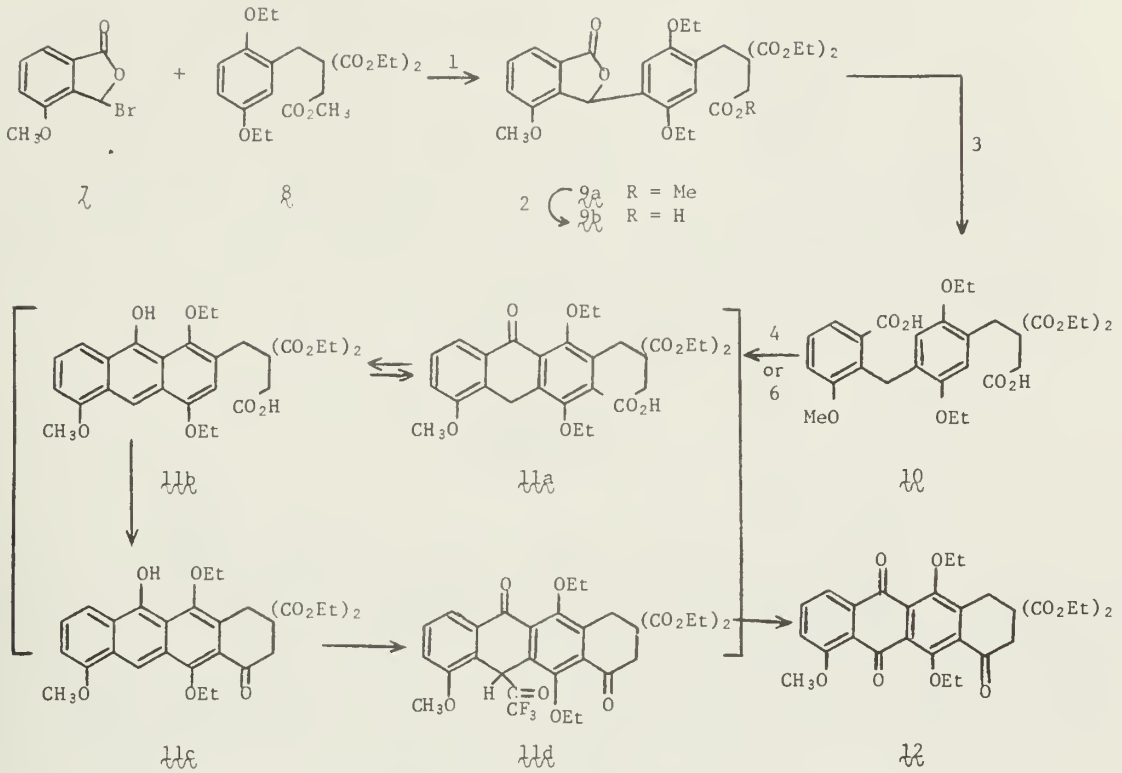
Friedel-Crafts Routes

One of the more recent regiospecific total syntheses of (±) daunomycinone by F. Johnson and his group at New York State University establishes the tetracyclic ring system and incorporates the C-7 oxygen atom in one step (ring DB → DCBA) via a novel Friedel-Crafts double cyclization reaction (Scheme 2).[9] Unfortunately, the stereochemical control in ring A functionalization yielded (±) 7-epidaunomycinone rather than (±) daunomycinone (for interconversion see above). Support for intermediates 11a-d comes from the upfield shift of C-4-OMe singlet in proton nmr (δ4.06ppm → δ3.97ppm) that occurs in the shift of equilibrium from 11a to 11b, and in structure 11d the hydrogen on C-5 was observed at 6.50ppm (as expected for proposed structure), as well as by precedent.[11]

The functionalization of the A-ring was conducted in six steps as shown in Scheme 3. The authors explain the stereoselective hydrolytic decarboxylation to trans substituted ketone 16 as a result of complexation of H_2O by the C-7 hydroxyl group which then delivers a proton to the α-face of the intermediate enol. The stereoselectivity in the hydroxylation step (5) is explained by steric control or neighboring group participation by the C-7 hydroxyl group. In Johnson's earlier work, the A-ring was first closed (structure 9, Scheme 2) followed by removal of the C-7 oxygen (to prevent aromatization), then closure of the D-ring which overall required many more steps.[11]

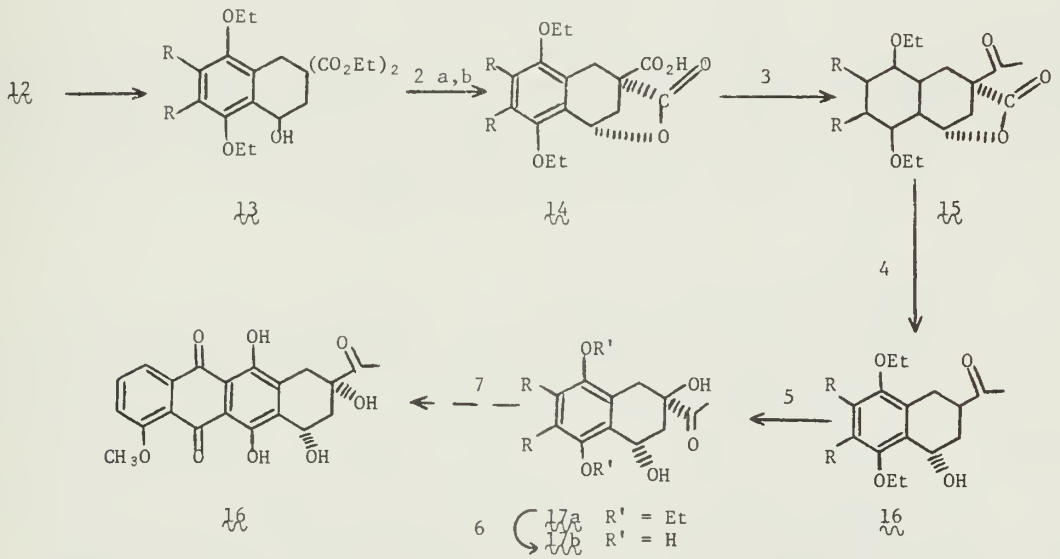
An earlier regiospecific synthesis by Kende utilizes the Photo-Fries rearrangement to help form the C-ring by keeping the C4-methoxy and A-ring substituents in the required juxtaposition (ring D + BA → DCBA, Scheme 4).[12]

Scheme 2.



Conditions 1) $SnCl_4$, CH_2Cl_2, 25°C, 6h, (94%) 2) NaOH/MeOH/THF/H_2O reflux, 4 days 3) CF_3CO_2H, Et_3SiH, 24h 4) $CF_3CO_2H/(CF_3CO)_2O$, 6h 5) 11d → 11c $NaHCO_3$ work-up then 6b. 6)a) $CF_3CO_2H/(CF_3CO)_2O$, 18h. b) CrO_3/HOAc/Acetone, 0°, 30 min, (46% from 10)

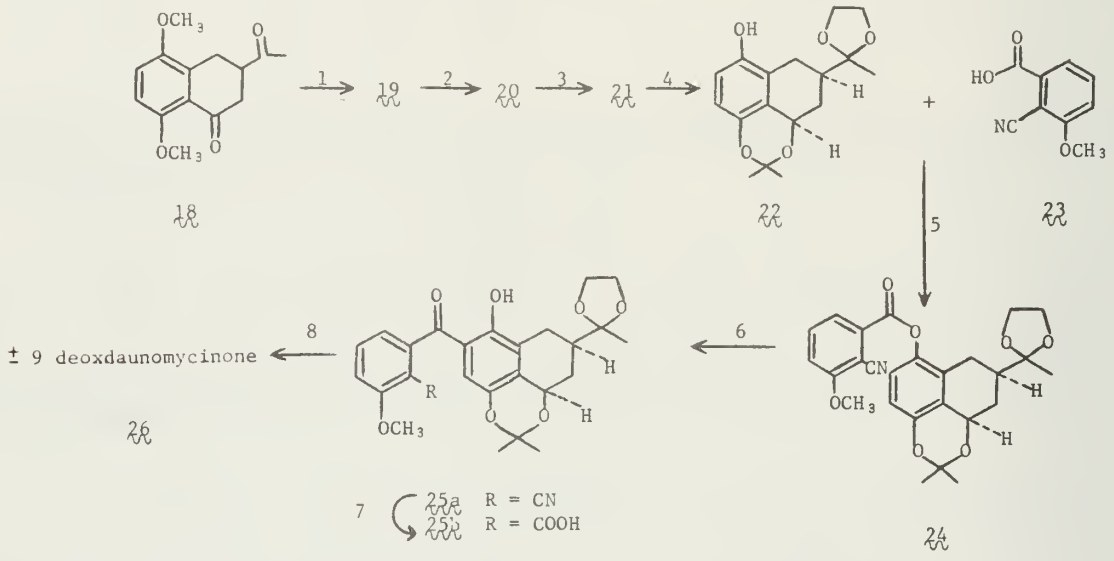
Scheme 3.



Conditions 1) BH_3, R.T., 30 min (79%) 2) a) NaOH,THF, 48h. b) $(CF_3CO)_2O$ (85% overall) 3) $SOCl_2$; CH_2N_2; HI (78%) 4) NaOH, H_2O, THF, 12h. (78%) 5) potassium t-butoxide/t-butanol/DMF/O_2/$(EtO)_3P$/-40°C/15min (40%) 6) $AlCl_3/PhNO_2$/2h. (64%) 7) epimerization-CF_3COOH (not attempted).

The precursor 24 was obtained via a five step sequence from the dihydroxytetralone, The Photo-Fries rearrangement was accomplished using a medium pressure Hanovia light source in 48% yield based on ester consumed, plus 47% recovered starting material. Further irradiation results in destruction of product. The use of benzene or acetonitrile as solvent, of triplet quenchers, of Pyrex vessels, or photolysis on a silica gel support has given no improvement in the chemical yield. The nitrile 25a was hydrolyzed to the corresponding acid and closed with liquid hydrofluoric acid which also removes the protecting groups to give (±) 9-deoxydaunomycinone. The 9-hydroxyl group was not incorporated, however, a procedure by Sih et al. introduces the C-9 hydroxyl via enol acetate and epoxidation (C-7 hydroxyl might have to be protected).[13]

Scheme 4.

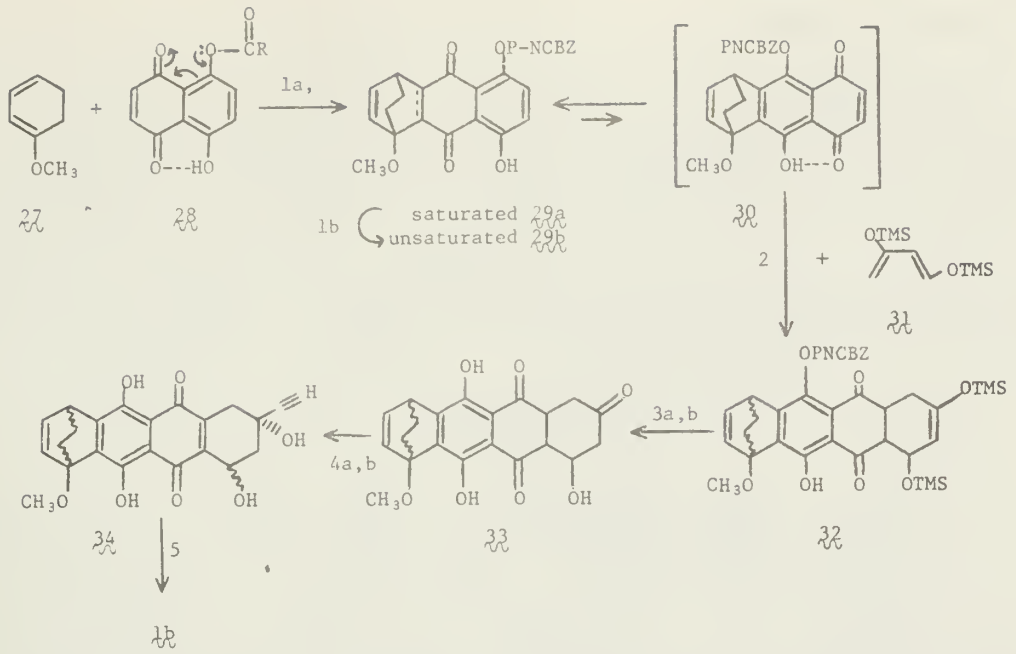


Conditions 1) BBr_3, CH_2Cl_2, -78°C to 0°C, 25 min. (76%) 2) Ethylene glycol, P-TSA, benzene, 4h., reflux (91%) 3) $NaBH_4$, reflux, 16h. (83%) 4) 2,2-dimethoxypropane, P-TSA, 25°C, 2h (88%) 5) Brewster Cioti method (77%) 6) 1% soln in dioxane, 70°C, hν (48%) 7) 10% NaOH: 10% Ethanol: 80% H_2O, reflux, 90 min. (~100% 8) a) HF, 20°C, 15 min. b) -60°C, $CHCl_3$, $NaHCO_3$(23%).

Diels-Alder Routes

The Diels-Alder route has been used extensively in the synthesis of 4-demethoxydaunomycinone but has not been exploited as much in regiospecific total synthesis of (±) daunomycinone itself.[4] One of the more ingenious approaches to (±) daunomycinone came from the labs of T.R. Kelly et al. at Boston College (Scheme 5).[14] The synthesis utilizes the phenol protecting group p-nitrocarbobenzoxy (P-NCBZ) as a directing substituent in a Diels-Alder reaction. The p-nitrocarbobenzoxy can be transferred intramolecularly in a tautomerization to direct a second Diels-Alder reaction by the selective trapping of the minor more reactive tautomer (steps 1 & 2, Scheme 5). The synthesis of compound 33 from starting material 28 can be carried through without purification in 89% yield (isolated by trituration >95% purity), and can be conducted on a multigram scale.

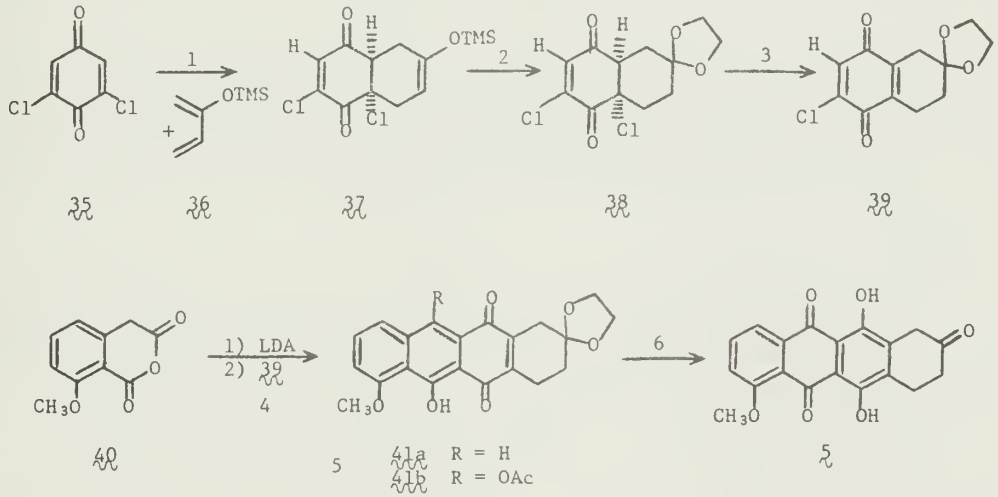
Scheme 5.



Conditions: 1) a) CH_2Cl_2, 20°C b)≤1 equiv. KH, PbO_2(XS), THF 2) CH_2Cl_2, 25°C, 48h. 3)a) 3NHCl, 3% H_2O_2, THF b) Zn, HOAc, THF, 0°C (89% yield from 27 + 28). 4)a) HC≡CMgBr (XS) b) O_2, $NaHCO_3$(aq), THF 5)a) thermolysis, xylene, 145°C, 30 min. (89%) 5b) 40% H_2SO_4, $HgSO_4$, THF (75% yield of 83:17 ratio of daunomycinone and its 7-epimer).

A recent regiospecific Diels-Alder approach by Tamura uses two Diels-Alder reactions as key steps in the synthesis of tetracyclic ketone 5 (see above) which is a common precursor to (±) daunomycinone (Scheme 6).[15] The first Diels-Alder reaction of 2-[(trimethylsilyl)oxy]butadiene 36 with 2,6-dichlorobenzoquinone 35 leads to adduct 37 which is transformed by mild acetalization and dehydrochlorination to give the ring-BA component 39 in 65% overall yield. The second Diels-Alder forms the desired tetracyclic DCBA ring system by reacting the lithium salt of homophthalic anhydride 40 with ring-BA component 39 to form adduct 41a regiospecifically in 65% yield. The adduct 41a is further elaborated to give tetracyclic ketone 5 in 38% overall yield from 39 and 40.

Scheme 6.

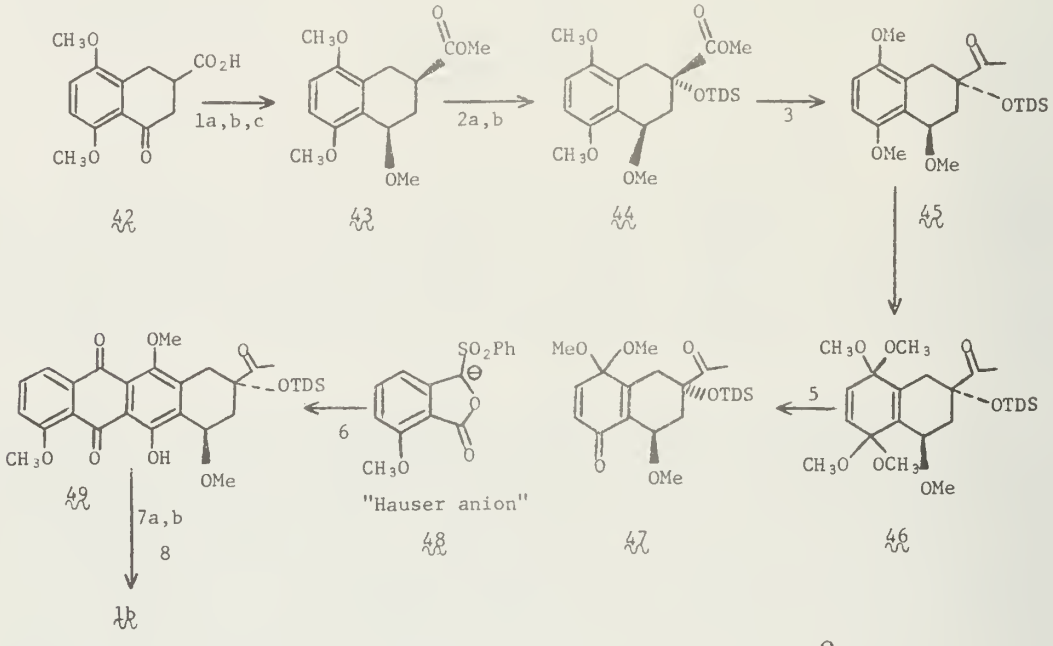


Conditions: 1) ether or benzene, 35-60°C, 3-6h. 2) ethylene glycol, cat. HCl, ether, R.T. 5h. 3) $(Et)_3N$, R.T., 2h (65% overall steps 1-3) 4) LDA+ 40 at -78°C + 39 → R.T. for 20 min (65%). 5) $Pb(OAc)_4$, AcOH-CH_2Cl_2, R.T., 16h (61%) 6) CF_3CO_2H-H_2O(2:1), 50°C, 6h (95%).

Nucleophilic Routes

The nucleophilic approach has proven to be very successful in controlling the regiochemistry of the A and D-ring substituents as evidenced by the regiospecific routes of Swenton and Parker. In Swenton's nucleophilic route the AB-rings are first synthesized with the A-ring fully functionalized and the B-ring in the form of a quinone monoketal (Scheme 7).[16] Combination of the AB fragment with the Hauser anion 48[17] gives the protected (±) daunomycinone in 50% yield. This was deprotected in two steps (both >90% yield) to give (±) epi-7-methoxy-7-deoxydaunomycinone which can be converted to (±) daunomycinone by solvolysis.[18]

Scheme 7.



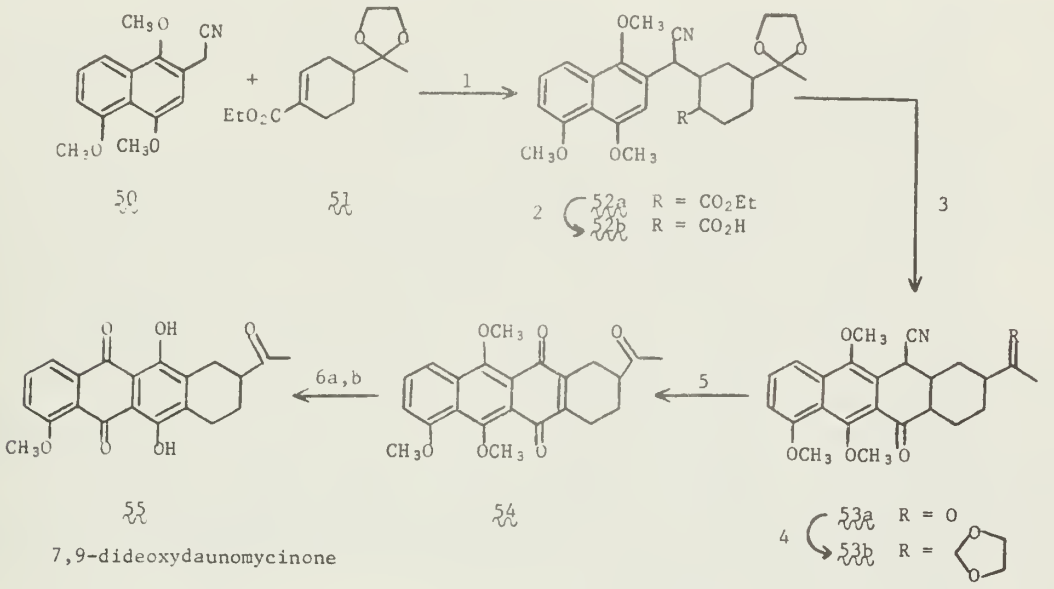
Conditions: 1)a) $NaBH_4$, EtOH b) NaH, MeI (ROR) c) CH_2N_2(RCOR) 2)a) LiCA, MoOPH (45% overall yield) 2b) TDSCl, pyr, DMF 3) $LiCH_2SOMe$, KF, $Al(Hg)_4$) anodic oxidation (96%) 5) Acetone: HOAC (4%)(2:1), 0°C, 1h(79%) 6) Dimsylate anion, THF (DMSO), 10 min. 0°C, 3h R.T. (50%) 7)a) BCl_3, -78°C, CH_2Cl_2, 45 min (>90%) 7b) $(Bu)_4N^{+}F^{\ominus}$, THF 8) Solvolysis wasn't reported - see ref. 18 for procedure.

A similar route by Hauser himself, uses the "Hauser anion" to form the DC-ring by addition to 5-ethoxy-2-furanone.[19] The ethoxy group of the DC-component can be transformed in two steps to give a second "Hauser anion" precursor. The second "Hauser anion" was condensed with 2-cyclohexen-1-one generating the tetracyclic system which requires many subsequent steps to reach (±) daunomycinone.

A second nucleophilic approach by Parker et al. involves the formation of the B-ring by a Michael addition reaction of naphthylacetonitrile 50 and α,β-unsaturated ester 51 to give compound 52 in 77% yield (Scheme 8).[20] Basic hydrolysis of the ester followed by an intramolecular Friedel-Crafts acylation and reketalization gave nitrile 53b in 61% yield. Nitrile 53b was converted to the quinone function by successive treatment with two equivalents of lithium diisopropylamide, oxygen gas, and sodium bisulfite to give quinone 54. This can be converted to (±) 7,9-dideoxydaunomycinone 55 by treatment with silver oxide-nitric acid followed by aqueous sodium hydrosulfite (90% yield for the

two steps). This six step sequence provides 7,9-dideoxydaunomycinone in 22% overall yield from nitrile 50 and α,β-unsaturated ester 51 which can be converted to (±) daunomycinone by known methods.[10,13] The naphthylacetonitrile 50 was obtained in five steps from sultone[21] and α,β-unsaturated ester 51 was obtained in five steps from perillatine (31% overall yield).[20] Kende independently developed virtually the same approach.[23]

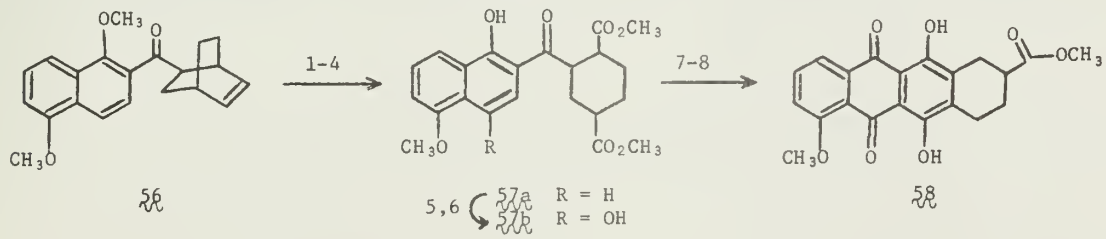
Scheme 8.



Conditions: 1) KH, THF, HMPA, 6h, -20° → 0°C (72%) 2) THF: EtOH (1:1), .1NKOH, reflux, 24h (77%) 3) $CF_3COOH/(CF_3C)_2O$ (1:1), reflux, 3h. 4) ethylene glycol, triethylorthoformate, P-TSA, benzene, 48h (98%) 5) 2 eq. LDA, THF: HMPA (10:1) -78°C -1h, O_2-1h, (60%) 6a) AgO, HNO_3 b) $Na_2S_2O_4$ (90%).

Sih's naphthalene route to anthracyclinones could be considered a combination of all three approaches (Scheme 9).[23] The key intermediate is the naphthalene derivative 56 which is prepared either by Diels-Alder or nucleophilic methods. The Diels-Alder reaction uses 1,3-cyclohexadiene with 1,5-dimethoxy-2-naphthylvinyl ketone and the nucleophilic approach uses 5-methoxy-tetralone and the acid chloride of a norbornene derivative. The naphthalene derivative 56 is then transformed by ozonolysis and subsequent steps (Scheme 9) to afford ketone 57 which after hydroxylation (45%), is cyclized by sulfuric acid in 41% yield to give ester 58. The ester 58 was not taken on to daunomycinone, however, others have hydrolyzed the ester to the acid and converted the acid to 7,9-dideoxydaunomycinone via the acid chloride and dimethylcuprate.[9]

Scheme 9.



Conditions: 1) O_3, KI 2) CrO_3 3) CH_2N_2 4) BBr_3 5) $Ce(NH_4)_2(NO_3)_6$ 6) $Na_2S_2O_4$ 7) H_2SO_4 8) CH_2N_2

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OBSERVATIONS ON THE MECHANISM OF THIOPHILIC ADDITION

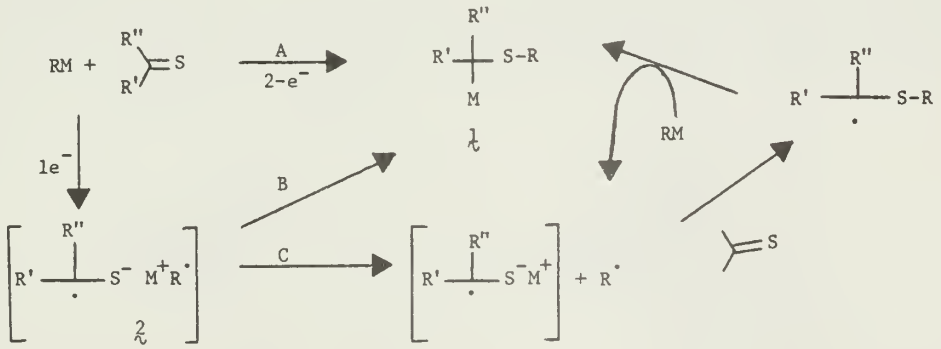
Reported by C. G. Garrett April 7, 1983

Addition to sulfur of thiobenzophenone by an organometallic to produce the α-thiaorganometallic 1 was first characterized as a general thiophilic addition in 1970.[1] Since then the reaction has been extensively investigated by a number of groups, shown to be quite a general process, and reviews have appeared.[2] The formation of 1 was demonstrated by trapping[3,4] while the fact that initial addition occurs at the sulfur was confirmed by a labeling study.[3] Later work has shown the extent of thiophilic addition to be a function of the thiocarbonyl, organometallic, and solvent.[2] To date, no study has provided unambiguous evidence as to the mechanism of formation of 1.

The three possible mechanisms which have been proposed[1,3] are shown in Scheme I. Path A depicts the simplest possibility: a direct two-electron addition of the organometallic to the sulfur atom of the thioketone to generate 1. Paths B and C propose initial formation of a caged radical ion pair 2 via single electron transfer (SET) from the organometallic to the thiocarbonyl. In Path B collapse of the radical pair within the cage would lead to carbanion 1. In the third path, C, a free radical chain process initiated by cage escape of the radical R· generated by the SET process is proposed.

Radicals have been detected in reaction mixtures of Grignard reagents and nonenolizable thioketones.[5] However, the studies have not demonstrated if the radicals detected lie on the main reaction path or are involved in some process not associated with thiophilic addition. Path C has been discounted by failure to observe isomerization of 1-propenyl organometallics in additions to thiobenzophenone under conditions where isomerization of the free 1-propenyl radical would be expected.[6] Solvent and temperature effects have been reported[7] on the thiophilic additions of phenyllithium and butyllithium to di-t-butyl and diphenyl thioketone with the observations rationalized in terms of the structures of the intermediate radical anion pairs 2. Current efforts to differentiate paths A and B of Scheme I on the basis of ring opening reactions of cyclopropylcarbinyl radicals will be presented.

SCHEME I



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A PROPOSED MODEL FOR THE CHIRAL RECOGNITION OF 1-(α AMINOALKYL)-2-NAPHTHOLS AND 1-(α AMINOALKYL) NAPHTHALENE

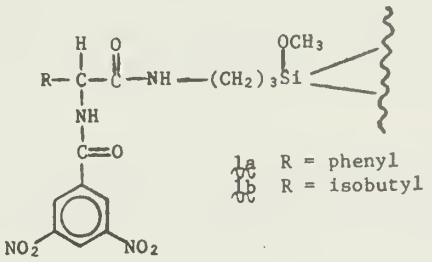
Reported by Karl Neidert April 11, 1983

The direct chromatographic resolution of racemic mixtures of enantiomers is of both theoretical[1] and practical importance. Enantiomers of a resolvable racemate exhibit different partition coefficients upon any chiral stationary phase (CSP) resulting in different retention times.

Theoretically one must have a minimum of three simultaneous interactions with a second chiral molecule if the stereochemistry of an enantiomer is to be "recognized." This is the so called "three point rule,"[2] first stated in terms of the interactions of a chiral substrate with a host receptor in 1933.[3] The three point rule is central to the design of successful CSPs.

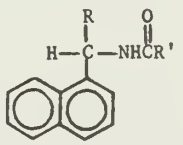
The list of racemic compounds resolved upon chiral liquid chromatography columns is rapidly expanding and includes chiral helicenes[4] and arenes.[5] Racemic mixtures of amino acids have been resolved by chiral crown ethers[6] and by ligand exchange chromatography.[7] Chiral polymers such as polyamides[8] and poly-(triphenylmethylmethacrylate)[9] have been successfully employed as CSPs.[10]

One of the more effective CSP's is derived from N-(3,5-dinitrobenzoyl)amino acids such as phenylglycine 1a or leucine 1b.

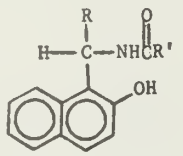


1a R = phenyl
1b R = isobutyl

These CSP's are capable of resolving a large variety of functionally different compounds.[12] The CSP's each contain a π acidic aromatic group, an acidic site and a basic site to interact with complimentry sites in molecules such as in 2 and 3. To aid in understanding the details of the chiral recognition mechanism involved in the resolution of 1-(α-aminoalkyl)-naphthalene 2 or 1-(α-aminoalkyl)-2-naphthol 3 on CSP's 1a and b, the structures of 2 and 3 were systematically varied. The effect of the variation upon chromatographic behavior was noted and several compounds in this series resolve extremely well. By the reciprocal principle a compound that resolves well should be considered a potential CSP. A CSP derived from 2 has been made and attempts to make a CSP from 3 will be discussed as well.



2



3

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THERMAL AND CHEMILUMINESCENT PROPERTIES OF AN AROMATICALLY-SUBSTITUTED MALONYL PEROXIDE

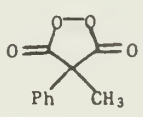
Reported by Judith E. Porter April 14, 1983

The phenomenon of solution chemiluminescence can be explained by three general mechanisms. The first is a direct process which involves the thermal rearrangement of a high energy molecule resulting in an electronically excited state product molecule. The best known example of this process is the system of 1,2-dioxetanes.[1,2,3] The second process is known as electrogenerated chemiluminescence (ECL) and involves an annihilation between electrochemically generated radical ions to form an electronically excited state product molecule.[4] The last system is known as chemically initiated electron-exchange luminescence (CIEEL) which is an indirect process involving electron transfer from an added activator to a peroxide, rearrangement of the peroxide radical anion, and back-electron transfer to produce the activator in an electronically excited state.[3c]

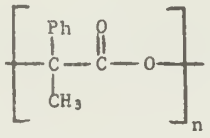
Since the CIEEL mechanism was first introduced by Schuster and co-workers in 1977,[5] a variety of peroxide systems have been shown to exhibit CIEEL behavior.[3c] The latest addition to this class of chemiluminescent peroxides has been malonyl peroxides.[6]

The first example of a malonyl peroxide was reported by Adam and co-workers in 1971.[7] Since that time, several other examples of malonyl peroxides have been reported and their thermal behavior has been intensely investigated.[8] However, one class of malonyl peroxide is conspicuously absent, that containing an aromatic substituent.

We have investigated the thermal and chemiluminescent behavior of an aromatically-substituted malonyl peroxide, 4-methyl-4-phenyl-1,2-dioxolane-3,5-dione 1. When thermolyzed, 1 decomposes cleanly to give quantitative



1



2

yield of polyester 2. In the absence of molecular oxygen, the catalyzed (by an aromatic hydrocarbon) thermal decomposition of 1 also gives polyester quantitatively. However, in the presence of activator and molecular oxygen, the decomposition yields acetophenone, polyester and light. Oxygen-18 labeling studies have shown that the oxygen atom in the acetophenone results from the incorporation of molecular oxygen.

The investigation into the chemiluminescent behavior of 1 has shown that it does exhibit CIEEL behavior in the presence of activators. The rate constants obtained for the catalyzed and uncatalyzed decomposition from chemiluminescent measurements agree with those obtained for the decay of 1 from FT-IR kinetic studies. These are given in Table I. This is good evidence that the decomposition of 1 is responsible for the observed chemiluminescence.

Table I.

Rate Constants for the Decay of 1*

	IR	Chemiluminescence
$k_{unimolecular}$	10.5 E-5 s^{-1}	9.6 E-5 s^{-1}
$k_{activated}$	1.2 E-2 s^{-1}	1.7 E-2 s^{-1}

* The activator used was perylene and the temperature was 70°C.

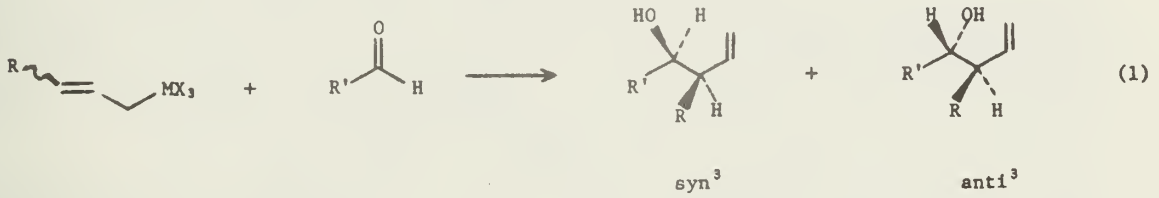
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ON THE STEREOCHEMISTRY OF ALLYLMETAL-ALDEHYDE CONDENSATIONS

Reported by Eric Weber April 18, 1983

Development of methodology for the control of stereochemistry in the synthesis of acyclic systems has become a primary goal of the synthetic organic chemist.[1] The synthesis of macrolide and ionophore antibiotics have provided much of the impetus for the development of such processes. The condensation of allylmetals with aldehydes has been shown to be one solution to this problem of stereochemical control (equation 1).[2]

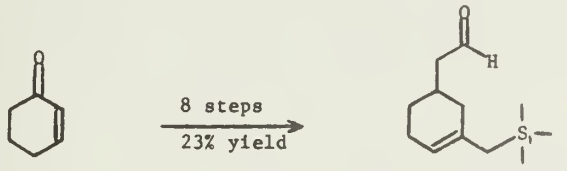


syn[3] anti[3] (1)

The high diastereoselectivity observed and the ease with which the resulting homoallylic alcohols can be transformed into other desirable compounds make this reaction very attractive. A variety of metals have been used, of which the most common include silicon,[4] tin,[5] boron,[6] chromium,[7] zirconium,[8] zinc,[9] aluminum,[10] and titanium.[11]

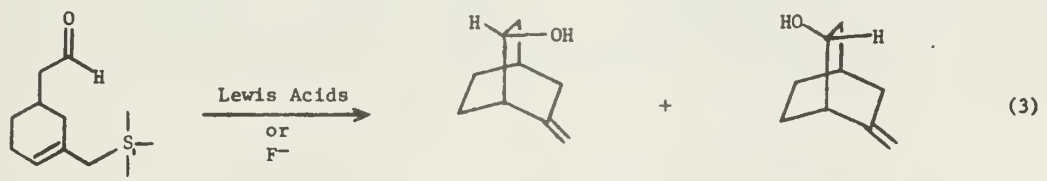
Although the synthetic value of this reaction has been thoroughly demonstrated, little is known about the factors which control its stereochemical outcome. An intriguing aspect of the reaction is the observed dependence of stereochemistry on the metal. Based on this observation, and taking into account reaction conditions, the allylmetals can be grouped into three types. Type I: syn/anti ratio of products reflects the Z/E ratio of the allyl moiety. Type II: syn-selective reactions independent of allyl geometry. Type III: anti-selective reactions independent of allyl geometry.

In an attempt to elucidate the role of the metal in these reactions, we have synthesized the model system 1 (equation 2) and have studied its cyclization with Lewis acids and fluoride ion (equation 3).[12] Intramolecular con-



(2)

1



(3)

1 2 3

densation of 1 results in the bicyclic alcohols 2 and 3, whose structures will provide direct information about the transition state geometry. We feel that

the synthetic approach to 1 is sufficiently versatile to allow for the incorporation and subsequent study of other metals (Sn, Cr, Zn). The synthesis of 1, the stereochemical analysis of 2 and 3, and the results of the cyclization and their implications will be presented.

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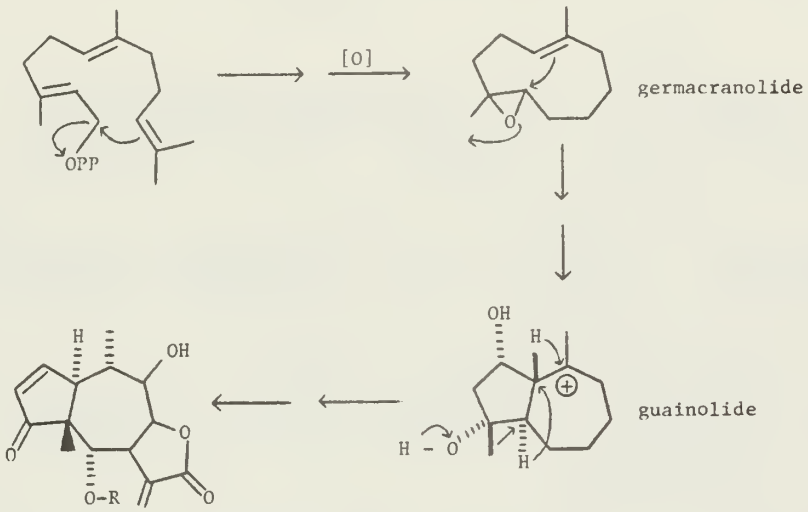
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TOTAL SYNTHESES OF PSEUDOGUAIANOLIDES

Reported by Athanasios Tsipouras April 25, 1983

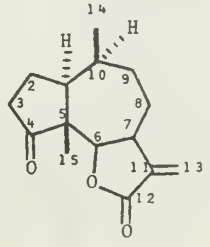
Among the many isolated sesquiterpene lactones, the pseudoguaianolides represent the largest family, more than 150 being described in a recent review.[1a]

The pseudoguaianolides are derived *in vivo* from farnesyl pyrophosphate by two successive cyclizations, first to germacranes and then to guaines, along with multiple oxidations.[2] At some stage in their biosynthesis, a complex rearrangement sequence occurs, in which 1,2-methyl migration converts the isoprenoid guaiane skeleton into the non-isoprenoid pseudoguaiane.

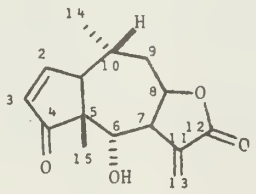


The pseudoguaianolides show significant biological activity, the antineoplastic activity of many members of the family both in vivo and in vitro being of special interest.[3] It has been suggested that the biological activity of these compounds arises from their ability to act as alkylating agents by virtue of Michael addition of sulfydryl enzymes to the electrophilic α,β unsaturated carbonyl function.

Two major varieties of pseudoguaianolides exist: ambrosanolides, which are characterized by a β-oriented C-10 methyl group and exemplified by damsin (1) and helenanolides which are characterized by an α-oriented C-10 methyl group, helenalin (2) is an example. The helenanolides being usually more functionalized than ambrosanolides possess greater biological activity and at the same time present a greater challenge to the synthetic organic chemist.



Damsin 1



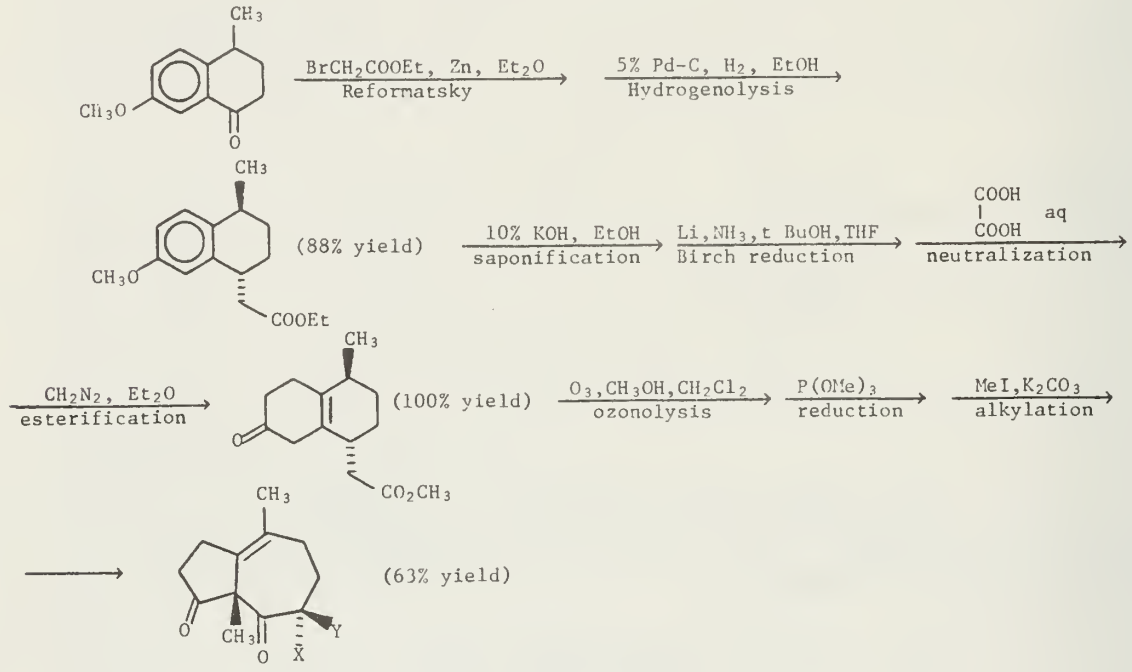
Helenalin 2

In recent years the total syntheses of many members of the pseudoguaianolide family have been accomplished. The syntheses of damsin, helenalin, mexicanin, carpesiolin, aromatin, aromaticin and confertin are briefly described in the present abstract.

Damsin[4a]

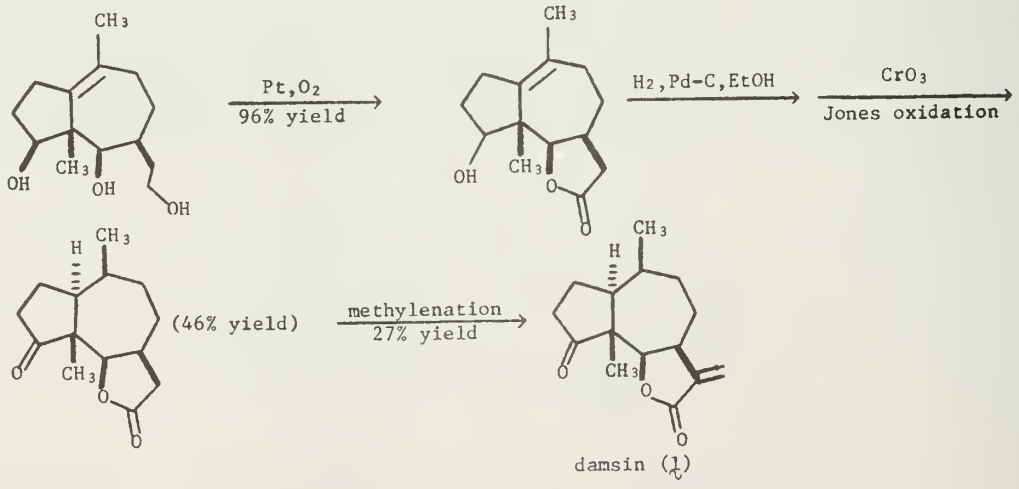
The first reported pseudoguaianolide synthesis was that of damsin (1) by Kretchmer and Thompson in 1976. Their approach involved construction of a 5,7 ring system after degradation of a 6,6 ring system.

Scheme 1



The desired compound in which X=H, Y=CH_2COOH was obtained together with the isomer in which X=CH_2COOH, Y=H (in a 2:1 ratio). Separation involved column chromatography followed by fractional crystallization. Reduction ($NaBH_4$) proceeded from the less hindered side (α side) to give the triol (62% yield) which was converted into the desired lactone as shown in Scheme 2.

Scheme 2



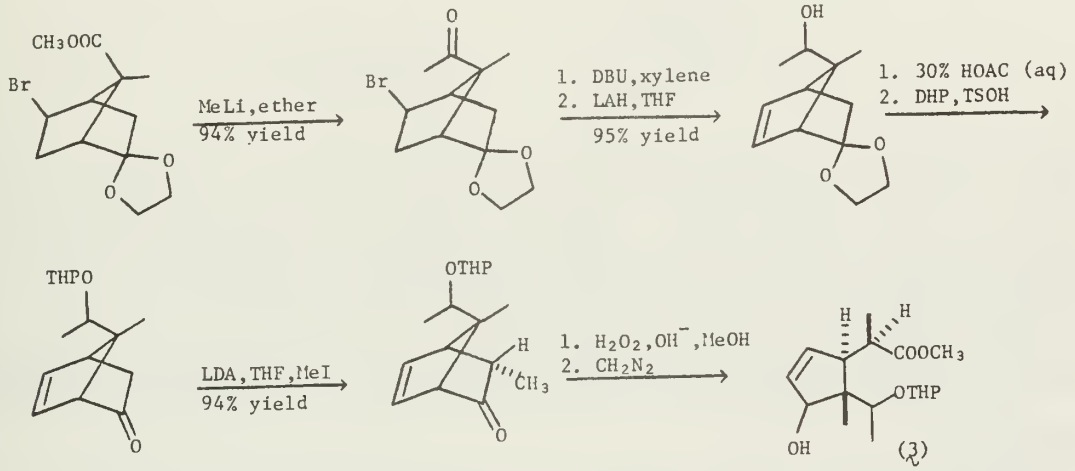
Introduction of the α-methylene group involved protection of the carbonyl functionality as the ketal, treatment with ethyl formate and sodium hydride followed by reduction with sodium borohydride, hydrolysis of the ketal with 3N HCl, reaction with p-toluenesulfonyl chloride in pyridine to give a tosylate which upon elimination of p-toluenesulfonic acid gave damsin.

The synthesis required 10 steps and the overall yield was 2-4% (from 4-methyl-7-methoxytetralone).

Helenalin

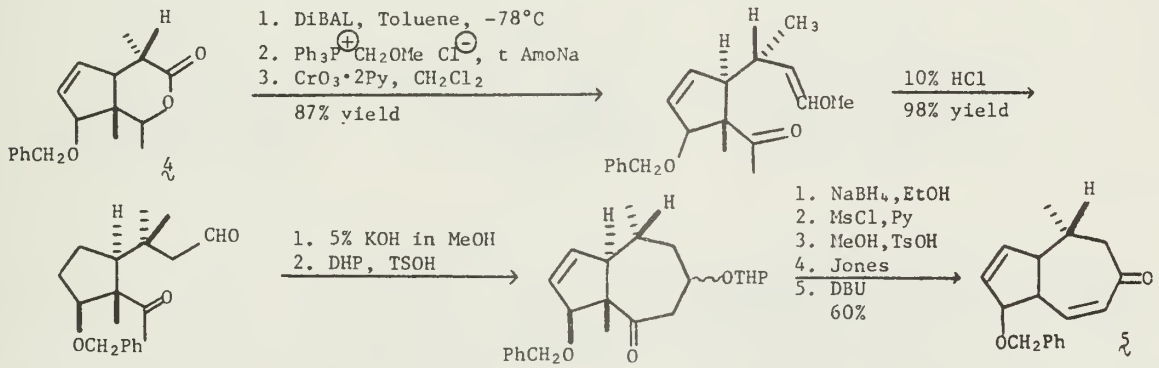
The total synthesis of helenalin (2) reported by Grieco and coworkers in 1978 was the first total synthesis of an helenanolide.[8a] The starting point was cyclopentanoid intermediate (3) available as shown in Scheme 3.

Scheme 3

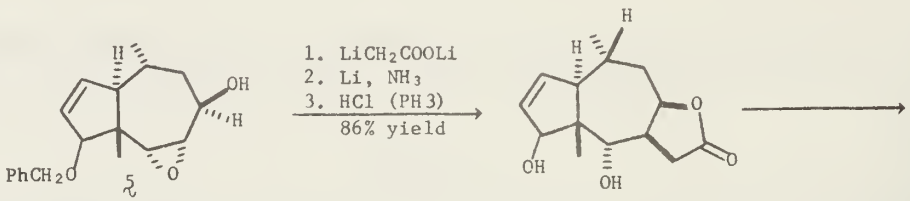


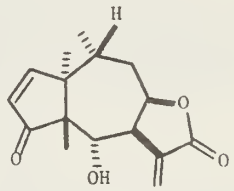
This intermediate was converted to lactone (4) in 65% overall yield by benzylation, cleavage of the tetrahydropyranyl and ester functionality and lactonization. The complete isomerization of the methyl group is not surprising in view of the severe 1,3 diaxial methyl-methyl interaction which exists in the initially produced lactone. The synthesis was continued as shown in Scheme 4.

Scheme 4



Epoxidation of the enone 5 with tert-butyl hydroperoxide in tetrahydrofuran containing Triton B gave in 93% α-epoxy ketone which upon reduction with sodium borohydride in ethanol gave exclusively in near quantitative yield epoxy alcohol 5.





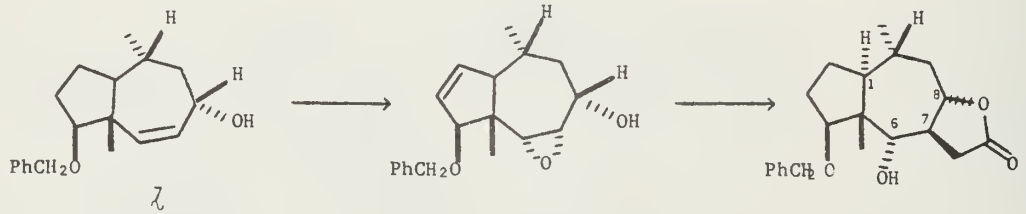
2 helenalin

α-Methylenation was performed on the corresponding bis(tetrahydropyranyl) ether (prepared in 82% yield) via hydroxymethylation, mesylation and β-elimination in 61% overa-l yield. Removal of the protecting groups gave a 78% yield of a crystalline diol which was oxidized by manganese dioxide to dl-helenalin (2) (yield of this final step: 69%).

The complete synthesis required 25 steps from intermediate 3 and went in 8% overall yield (or 2% overall yield starting from norbornadiene).

Mexicanin[11]

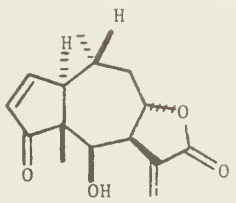
The finding that LAH reduction of hydroazulenone 5 goes in a completely stereospecific fashion to afford hydroazulenol 7 allowed Grieco and coworkers to extend their projected synthetic scheme for the total synthesis of helenalin to the total synthesis of mexicanin 8 as well. Thus epoxidation of hydroazulenol 7 (MCPBA, CH_2Cl_2) gave syn epoxy alcohol in 65% yield. Treatment of the epoxide with the dianion of acetic acid gave tricyclic lactone in 82% yield.



7

Formation of C(6) β-oriented alcohol was achieved, in 70% yield, by Jones oxidation followed by reduction with sodium borohydride. Removal of the benzyl group was effected with Li, NH_3 after protection of the free hydroxyl group as a tetrahydropyranyl derivative and saponification of the lactone. Relactonization gave a 75% yield of a lactone. α-Methylenation (1. LDA;HCHO 2. MsCl, Py; 3. DBU) of the tetrahydropyranylated derivative went in 56% yield. Finally, cleavage of the protecting groups (86% yield) and oxidation with manganese dioxide (78% yield) gave dl-mexicanin 8.

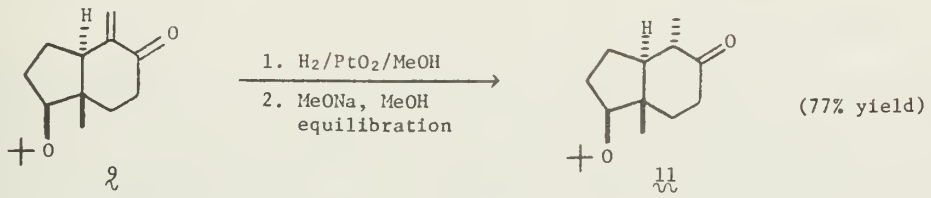
The complete synthesis required 8 steps from intermediate 5 and went in 10% overall yield.



Mexicanin 8

Carpesiolin[9b]

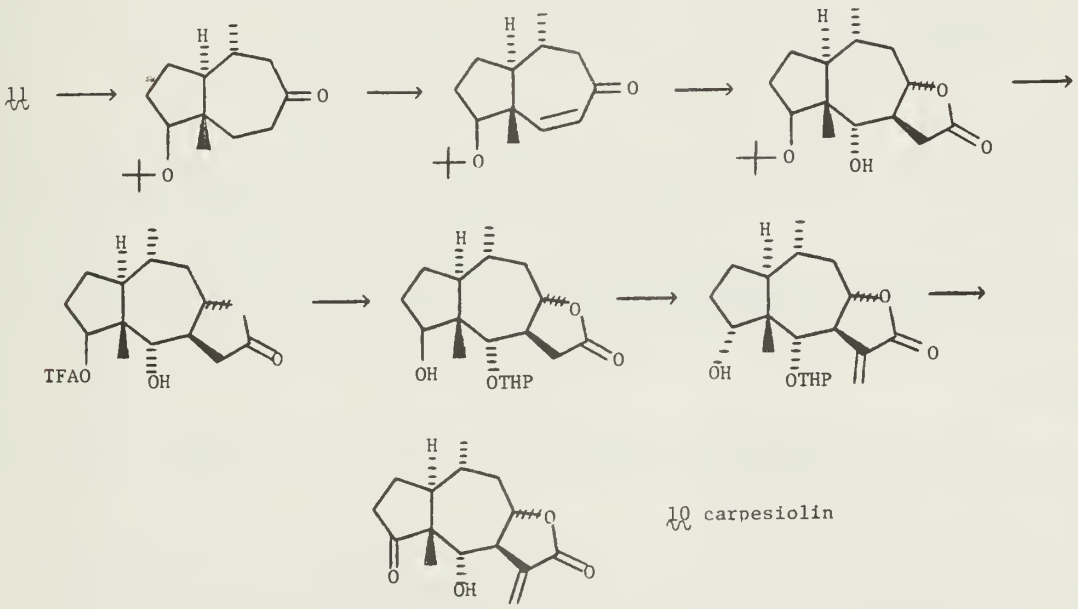
The total synthesis of carpesiolin by Kim and coworkers starts with literature compound 9.



9 11

Regiospecific ring expansion was effected by using Nozaki's procedure, reaction of 11 with dibromomethyllithium generated in situ [LDA-CH_2Br_2/THF/ -78°C], followed by treatment with butyllithium gave the perhydroazulenone in 40% yield. The regiospecific introduction of the double bond was accomplished using phenylselenylation-deselenylation [i) LDA/THF, PhSeBr; ii) H_2O_2/THF] in 68% yield.

The synthesis was completed much in the same way as Grieco's syntheses of Helenalin and Mexicanin.

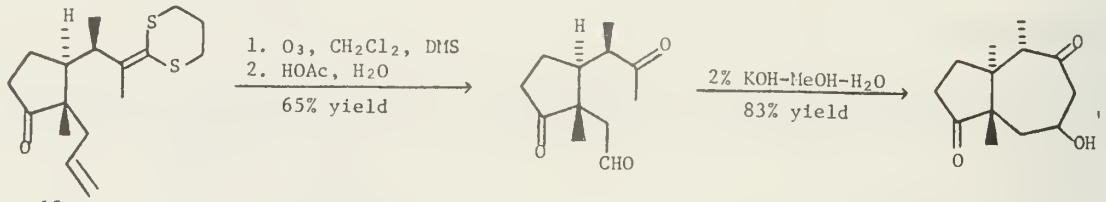


10 carpesiolin

The synthesis required 11 steps and went with 2% overall yield (from compound 9).

Aromatin[10b]

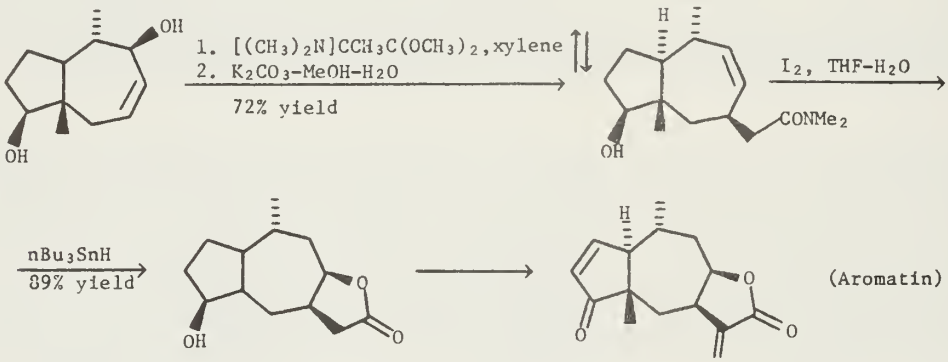
The approach to aromatin, by Ziegler and Fang, is based on their finding that anions resulting from ketene dithioacetals give γ-carbon Michael addition products with α,β-unsaturated compounds. Thus metalation of the dithiane of (E)-2-methyl-2-butenal, treatment of dithianylidene derivative with 2-methyl-2-cyclopentenone and alkylation of the resultant ketone enolate as its cuprous salt, with allyl bromide provided ketene dithioacetal 12 in 50% yield.



12

The hydroazulene derivative obtained as shown, from 12, by ozonolysis and aldol condensation was dehydrated to the conjugated enone (P_2O_5 - CH_3SO_3H) and reduced to a diol (LAH, stereoselective α attack) in 49% yield. Introduction of the C_7 β-acetic acid, by using the Eschenmoser variant of the Claisen rearrangement, iodolactonization and reductive dehalogenation gave 13 as shown in Scheme 5.

Scheme 5



Treatment of lactone with Bredereck's reagent $[(CH_3)_2N]_2CHOCH_3$ followed by DIBAL reduction resulted in methylene incorporation in 98% yield.

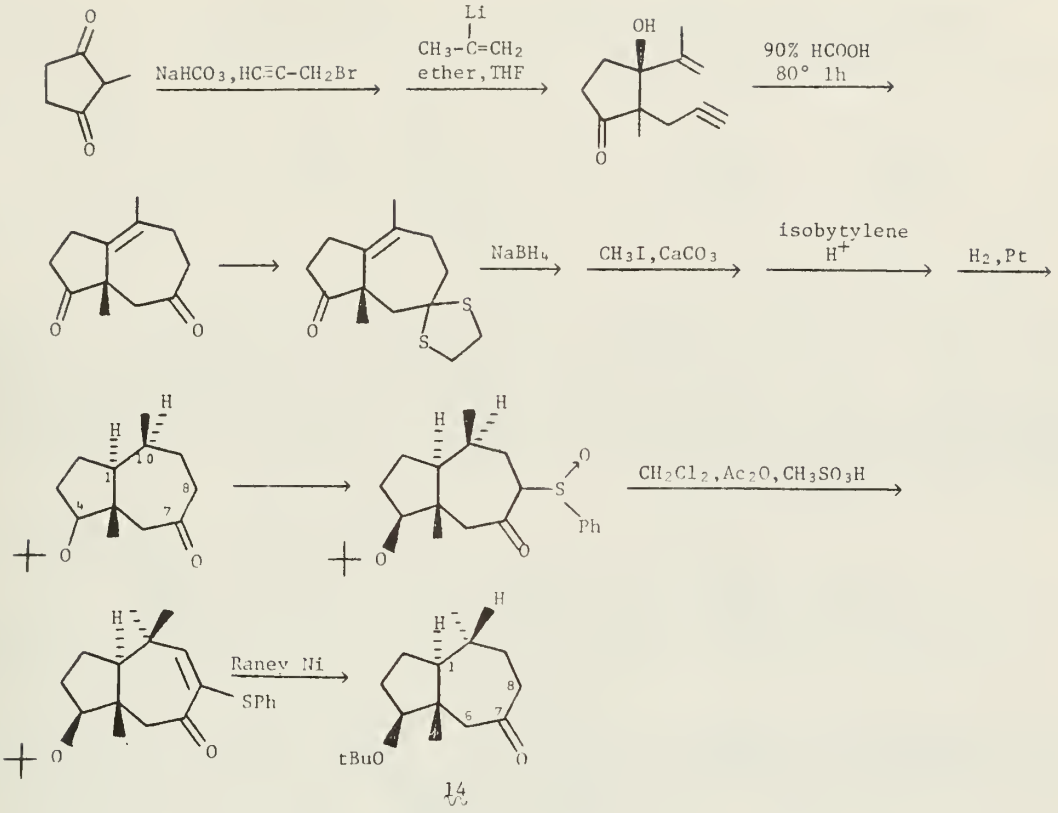
The synthesis was completed with pyridinium chlorochromate oxidation to (+) 2,3 dihydroaromatin (quantitative yield) and finally introduction of the 2,3 double bond via selenylation-selenoxide elimination (52% yield).

Aromaticin[11]

The aromaticin synthesis described by Lansbury and coworkers uses hydroazulene derivative 14.

As shown in Scheme 6 an acetylenic cycloheptanone annelation is followed by inversion of configuration at C-10 achieved by rendering C-10 hydrogen vinylogously enolic, to give compound 14.

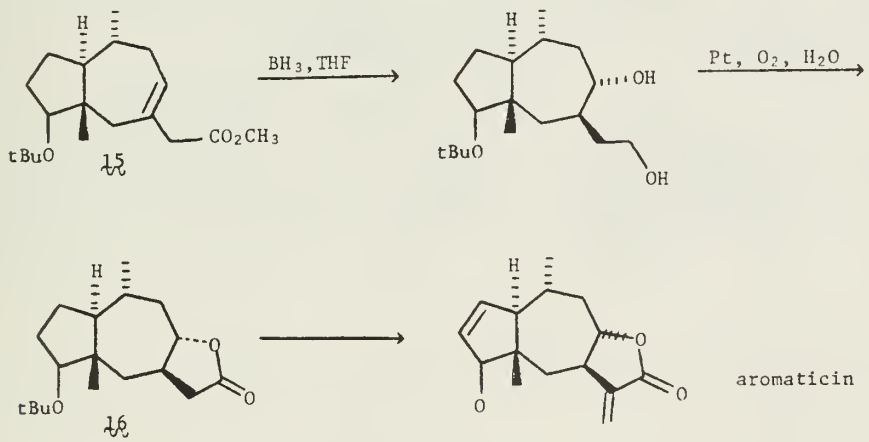
Scheme 6



14

The lactone annelation commenced with carbanion attack at C-7 of 14 (methyl trimethylsilylacetate and LDA, quantitative yield). Once the acrylate side chain had been introduced deconjugation toward C-8 was cleanly achieved by protonolysis of the kinetic dienolate resulting from LDA-induced proton abstraction to give 15 which was transformed to lactone 16 as shown in Scheme 7.

Scheme 7

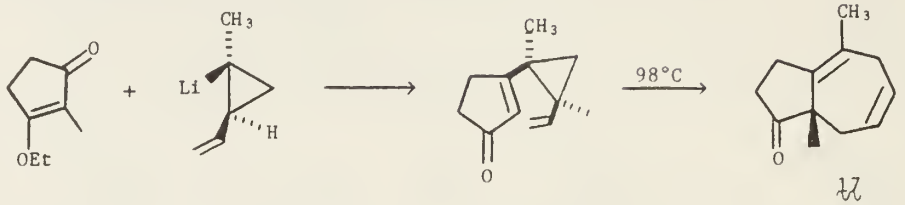


15 16

Incorporation of the methylene group was achieved by alkylation with methoxymethyl bromide, followed by treatment with unsolvated potassium tert-butoxide, potassium hydroxide in THF effecting methanol elimination. Deblocking and oxidation of the C-4 alcohol functionality gave 2,3 dihydroaromaticin and the double bond was introduced via selenylation, selenoxide elimination.

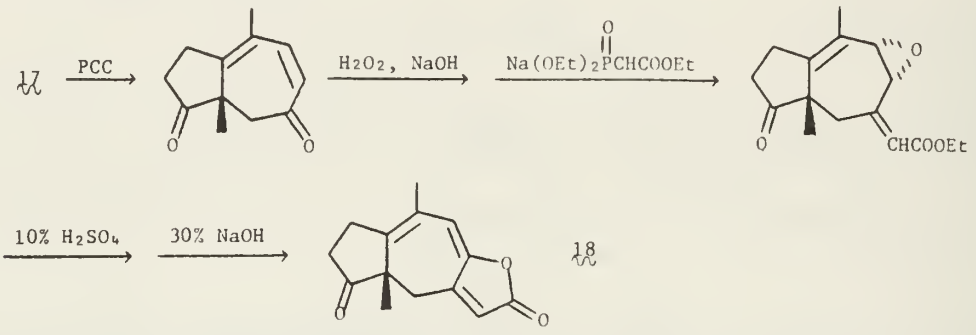
Confertin[5c]

Compound 17 prepared as shown, was used by Wender and coworkers in a total synthesis of confertin.

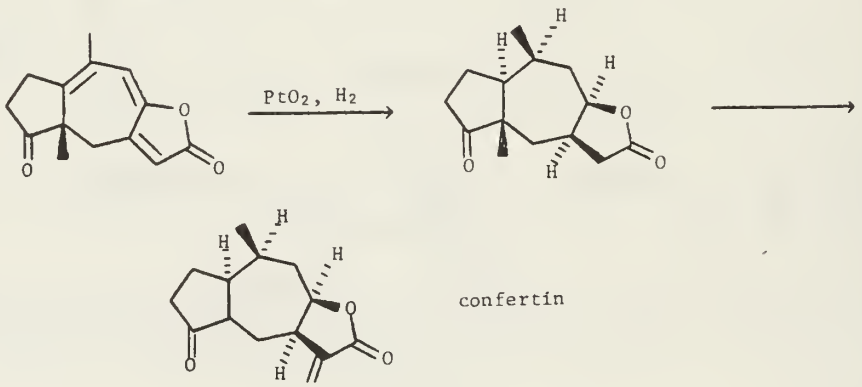


17

Upon oxidation with pyridinium chlorochromate (PCC) dienone was obtained in 63% yield. Treatment with basic hydrogen peroxide afforded a single epoxy ketone and olefination in benzene gave the Z-unsaturated ester with stereoselectivity greater than 95%. On exposure to acid and then treatment with base lactone 18 was formed.



Hydrogenation went with stereoselectivity greater than 80%. Methylenation (1. $Me_2NCH_2^+I^-$, THF; 2. MeI, MeOH; 3. $NaHCO_3$ (aq); 4. 10% H_2SO_4 (aq)) gave confertin.



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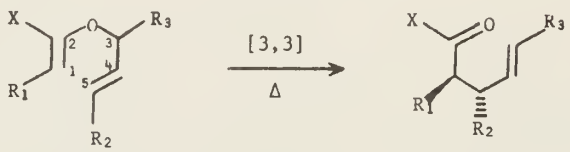
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CARBANION ACCELERATED CLAISEN REARRANGEMENTS

Reported by Michael Harmata April 28, 1983

The Claisen rearrangement (cf. Scheme 1) has developed over the past several decades to an extremely powerful synthetic tool.[1a-c] The γ,δ unsaturated carbonyl compounds produced by this [3,3] sigmatropic rearrange-

Scheme 1.



X	T°C
H, alkyl	160-200
OR	135
NR_2	110-140
OLi, OTMs	25-67
$ZCH^{\ominus}$	?

Z = carbanion stabilizing group

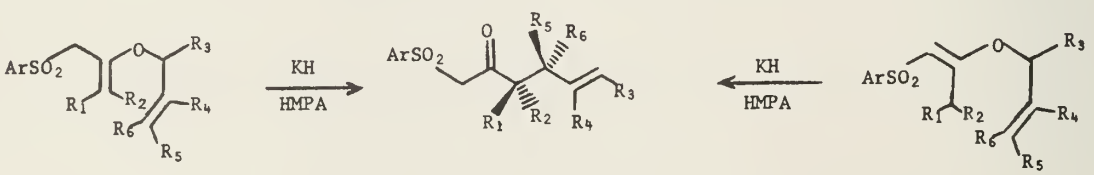
ment contain complimentary functionality, allowing subsequent transformations to be performed with relative ease. In addition, the rigid transition state of the process leads to high stereoselectivity in the newly formed double bond (mostly E), and well-defined stereochemical relationships between substituents on tetravalent carbon atoms (R_1, R_2; Scheme 1) of the product.[2a-c,3] All these factors make the Claisen rearrangement ideally suited for natural product synthesis.[1b]

Recently, renewed interest has arisen concerning substituent effects on the Claisen rearrangement.[4a-g] This has been due in part to the desire to find increasingly mild variants of the reaction applicable to acid or heat sensitive molecules. We have invented a regioselective variant that is mild and produces γ,δ unsaturated ketones as products.[5,6]

Initial unsuccessful experiments with resonance stabilized anions (Z = CO_2Et, CN; Scheme 1) prompted use to investigate the sulfone as anion stabilizing substituent (Z = SO_2Ar).

The allyl vinyl ethers used in this study, I and II, were synthesized by alumina catalyzed or allyloxide initiated addition of an alcohol to the appropriate arylsulfonyl allene.[7,8]

Treatment of allyl vinyl ethers I and II with KH in HMPA at 50°C or less



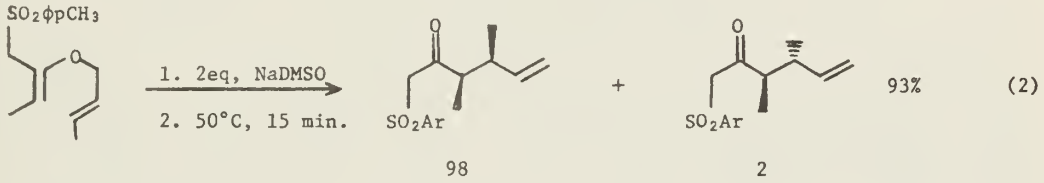
I III II

gave regiohomogeneous keto-sulfones III in good yields. Control experiments showed that anions are responsible for the rearrangement. The effects of

methyl substitution were studied and found to be in accord with the results of others.[4a] Several limitations of the reaction were discovered with respect to the nature of the allyl ether unit in the rearranging system.

Solvent and counterion effects on the rate of rearrangement of I (R_1-R_6 = H) were minimal, indicating only a slight change in the nature of the rearranging species as a function of these variables. In HMPA and DMSO, anions of I rearrange at almost identical rates (based on percent completion data) regardless of counterion. In THF, a reversed counterion effect was observed.

One of the most important findings in this research has been the discovery that C-1, C-5 disubstituted allyl vinyl ethers (I, $R_1 = CH_3$; R_5 or $R_6 = CH_3$) give rise to products very diastereoselectively and in the sense expected from the chair transition state of the Claisen rearrangement (eq. 2).[9]



98 2

Solvent and counterion studies with I ($R_1 = R_5 = CH_3$) showed a clear solvent effect and a small but noticeable counterion effect. Yields and selectivities for the compound derived from cis-crotyl alcohol (I, $R_1 = R_6 = CH_3$) were lower.

The direct formation of stabilized enolates by the carbanion accelerated Claisen rearrangement has broad synthetic implications, making this reaction a potentially very useful contribution to the organic chemist's arsenal of carbon-carbon bond forming reactions.

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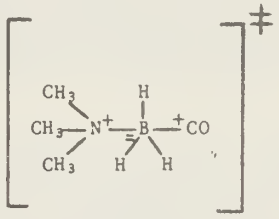
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HYPERVALENT BORON (10-B-5)[1] COMPOUNDS

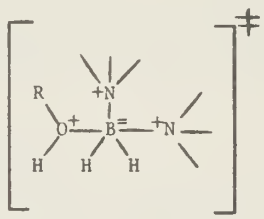
Reported by David Y. Lee May 2, 1983

Among the first row elements of the periodic table, only two have had reported examples of hypervalent species,[2] carbon[3] and fluorine.[4] Martin and Forbus[3] reported ^{13}C-NMR data and other electrochemical evidence for a stable 10-C-5 species. The F_3^- anion, the first 10-F-2 species, was observed by Raman and IR spectroscopy at low temperature in an argon matrix.[4]

Stable hypervalent boron compounds have never previously been isolated or directly observed. However, some kinetic studies of processes proceeding via pentavalent 10-B-5 transition state have been reported.[5] The kinetics of the gaseous reaction between borine carbonyl and trimethylamine was studied from 207.3 to 273.2 K. Reaction in this temperature range was found to be second order.[5a] An S_N2 mechanism was suggested for the bimolecular reaction. The transition state can be represented as 1. Another example was studied by Schelogeva and co-workers. On the basis of their experimental data, they postulated that the first stage in the solvolysis process, reaction between diamino boranes and alcohols, to be an amine displacement reaction.[5b] The experimentally determined activation entropies are highly negative (from -29.4 to -31.3 eu). In the presence of amines and alcohols, the authors feel that this implies a highly ordered 10-B-5 transition state; the most likely one being 2.



1



2

The previous success in application of proper ligand design[7] and the existence of the 10-C-5 species and the 10-F-2 species provide grounds for confidence that a stable 10-B-5 species can be directly observed or even isolated. Since a more electropositive σ-donor central atom has a larger stabilizing effect on charge distribution of trigonal bipyramidal (TBP) structures,[8] then a more electropositive element, such as boron, would form more stable hypervalent compounds than more electronegative elements, such as carbon and fluorine. In the carbon system, the most favorable case, that with the most electron-withdrawing apical ligands, the free energy of activation for the intramolecular associative displacement (S_N2 mechanism) was as low as 10 Kcal/mol.[3] For those 10-B-5 transition states above, the free energies of activation range from 8.6 to 20.0 Kcal/mol.[7] Because a carbon centered system with a comparable activation energy barrier was altered to render the closed pentavalent structure more stable than its open chain isomers, it seems feasible that alteration of a boron centered system would make the pentavalent boron structure the most stable.

The synthesis of a tridentate ligand, which has been designed[9,10] to offer sufficient stabilization to isolate a stable hypervalent boron compound, will be presented. It provides a) an apical ligand of great electro-

negativity, enhanced by the inductive effect of CF_3 groups, b) two apical-equatorial spanning five-membered rings, and c) an equatorial ligand neutralizing the negative charges on the central boron atom. Two ortho equatorial π-acceptor and σ-donor ligands are also included. All experimental data strongly suggest that the compound is the first stable, isolable pentavalent-boron species known.[11,12]

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SELECTIVE ISOMERIZATIONS USING IR MULTIPHOTON EXCITATION

Reported by Barbara Goodson May 5, 1983

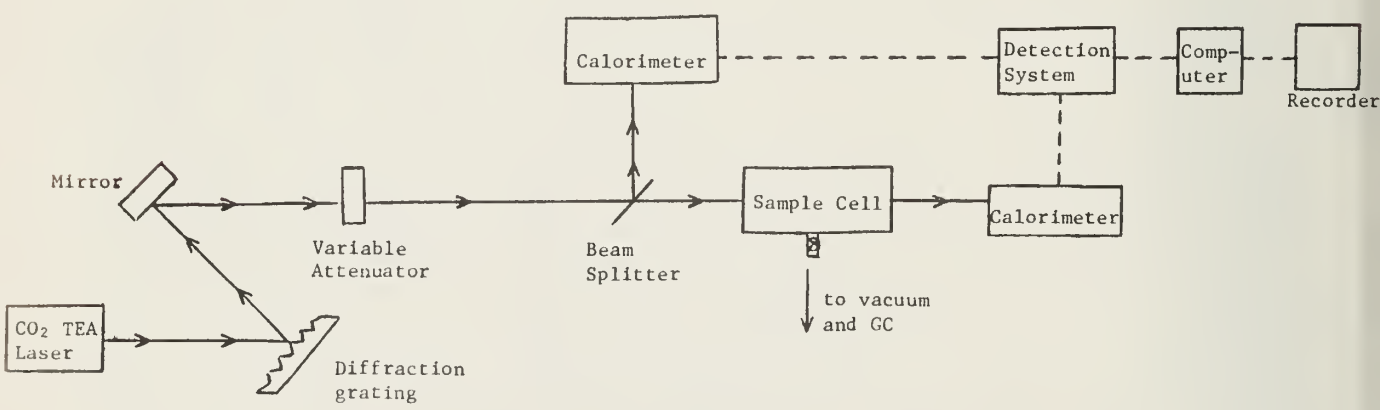
The creation of high-powered infrared lasers has generated a great deal of interest in the reactions of organic molecules subjected to an intense IR field.[1] The phenomenon of IR multiphoton excitation (MPE), which may be characterized as photochemistry in the ground electronic state, offers a number of advantages over other methods of molecular excitation of polyatomic molecules. These advantages include high selectivity, high excitation energy, and minimal role of thermal effects.

Much of the work in IR MPE has centered around its use in isotopic separations and in dissociation reactions of polyatomic molecules.[2] Multiphoton-induced isomerization has attracted interest only more recently. Current topics are focused upon IR MPE's potential as a probe for molecular dynamics[3] and possible synthetic applications (since the less-thermodynamically favored product is often selectively obtained).

A typical arrangement for an IR multiphoton isomerization experiment is shown in Figure 1. Irradiation of the sample is usually carried out by the use of a pulsed CO_2 TEA laser.[4] The energy of the laser beam is monitored by a detector such as a photoacoustic detector[5] or a calorimeter.[1] The effective laser fluence (energy density) is adjusted to $\sim$2-6 J cm^{-2} either by using an unfocused arrangement and collimating the beam with a Gallilean telescope, or only mildly focusing the beam and varying the position of the sample cell between the lens and the focal point. This is important because at high fluences dissociation products begin to appear. The gaseous sample is contained in a pyrex cell with NaCl or quartz windows. The irradiation frequency selected is usually one at which the reactants, but not the products, absorb strongly. Products are commonly monitored by GC or GC/MS.

Figure 1.

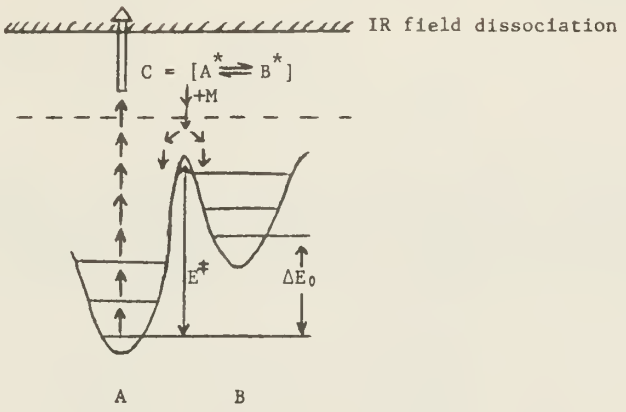
Typical experimental arrangement for IR MPE



The basic multiphoton isomerization process is shown in Figure 2 for the hypothetical reaction A → B.[16]

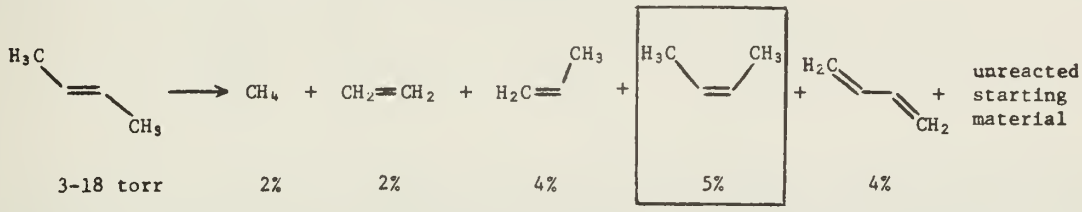
Figure 2.

Isomerization of A to B in the presence of buffer gas M by an intense IR field

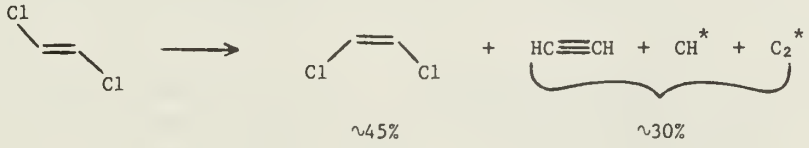


An intense pulse of IR radiation selectively excites a molecule of A above the reaction threshold energy $E^{\ddagger}$ by multiphoton absorption. Isomerization is very fast above the barrier and the two isomers may be regarded as representing adjacent regions in the phase space of the excited molecules $C = [A^{*} \rightleftharpoons B^{*}]$. The molecules are deactivated to form either A or B, either by intramolecular relaxation, or by collisions, such as with buffer gas molecules M (e.g. He) present in excess in the reaction mixture. The thermodynamics of such a system in which the presence of a buffer gas enhances yield has been worked out by Ben-Shaul and Haas.[16]

The earliest observation of IR multiphoton-induced isomerization was made by Yogev and Lowenstein-Benmair[6] in 1973, when they obtained a small amount of cis-2-butene along with fragmentation products upon irradiation of trans-2-butene. They also obtained enrichment of the cis-isomer upon irradiation of a mixture of the two isomers.

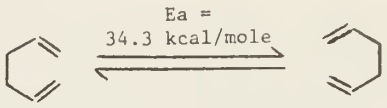


This work was followed by an investigation of trans-dichloroethylene by Letokhov and coworkers.[7] They observed the isomerization of trans-$C_2H_2Cl_2$ to cis-$C_2H_2Cl_2$ along with the production of both excited and unexcited dissociation fragments. They also investigated the effect of added buffer gases and shortening of the laser pulse tail on product distributions.

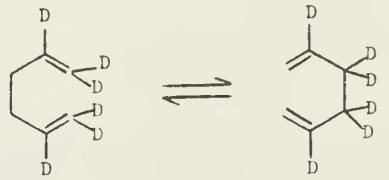


While neither of these early experiments resulted in clean yields of one product, they helped establish these processes as non-thermal in nature.

The first system in which the rate of isomerization is faster than the dissociation rate was studied by Yogev and Glatt in 1976.[8] They investigated the reversible Cope rearrangement of 1,5-hexadiene labeled with deuterium at various positions.



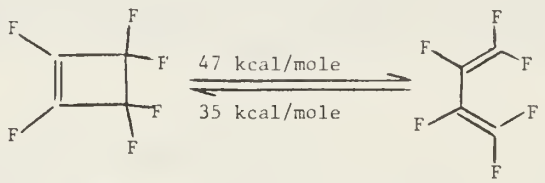
Irradiation of an equilibrium mixture of 1,5-hexadiene-1,1,2,5,6,6-d_6 (1) and 1,5-hexadiene-2,3,3,4,4,5-d_6 (2) with 5400 pulses at 5 torr resulted in complete conversion of (2) to (1) according to NMR.



1 2

Similar results were obtained for the other deuterated isomers. The high conversions indicated that the main process was indeed the unimolecular, single-step Cope rearrangement.

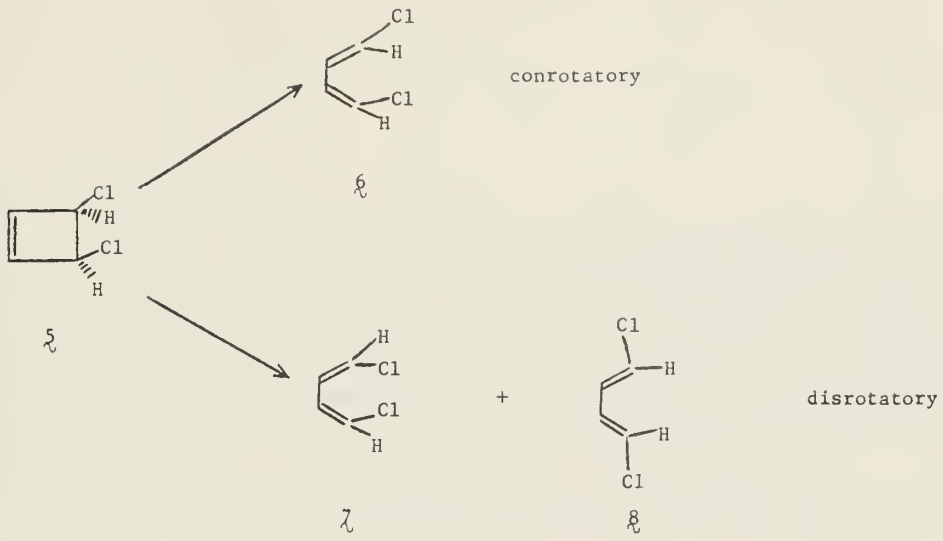
Another electrocyclic reaction that has been studied is the isomerization of hexafluorocyclobutene (HFCB, 3) to the less thermodynamically stable hexafluorobutadiene (HFB, 4).[9] By using an unfocused laser beam and an HFCB pres-



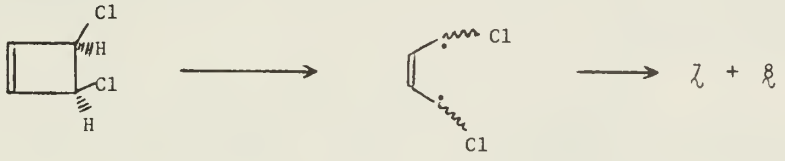
3 4

sure of 0.5 torr, Yogev and Benmair obtained 60% conversion of 3 to 4, which is the highest conversion of HFB obtained directly from HFCB without excitation with ultraviolet light. (Mercury-sensitized irradiation of HFCB with ultraviolet light gives HFB in high yields, which, unlike the IR irradiation, is contaminated with decomposition products). Addition of about 16 torr of He quenched the reverse reaction rate and the authors were able to perform quantitative conversion of HFCB to HFB. They explained this result as due to selective relaxation by the inert gas. Similar results were obtained when they studied the ^{13}C selectivity of this reaction.[10]

Two research groups have studied the isomerization of cis-3,4-dichlorocyclobutene to its open-chain isomer. They were particularly interested in the stereochemical outcome with respect to the Woodward-Hoffman orbital symmetry rules. The Woodward-Hoffman rules predict that the electrocyclic ring-opening of cis-3,4-dichlorocyclobutene (5) should be a thermally allowed, conrotatory process to produce 6 as the only isomer. This was confirmed experimentally by Danen, et. al.[11]

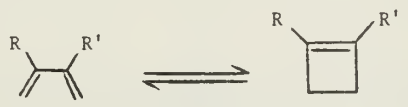


Since IR multiphoton processes are generally assumed to proceed through the ground electronic state, it was expected that IR irradiation of 5 would result in the production of 6. If the reaction proceeded through an electronically excited state one would expect to find 7 and 8. When Danen and coworkers[11] irradiated cis-3,4-dichlorocyclobutene with laser fluences ranging from 2.1 - 3.5 J cm^{-2} they obtained exclusively 6. They concluded that the reaction indeed occurs through the ground electronic state. Gordon, et. al.,[12] reporting in a preliminary communication, obtained the same results with laser fluences below 3.5 J cm^{-2}. However, at higher fluences small amounts of the symmetry-forbidden products 7 and 8 were detected; they found that the fraction of 7 and 8 increased with increasing laser fluence. They tentatively proposed that the forbidden products are most likely formed via a biradical intermediate, e.g.



Weitz, Lewis and coworkers have effected a number of isomerizations using IR MPE. When trans, trans-2,4-hexadiene was irradiated, a mixture of less-thermodynamically stable hexadienes was obtained, along with cyclopentadiene as a minor dissociation product.[3] Similar mixtures were obtained upon irradiation of other isomers.

These workers have recently achieved the efficient and selective isomerization of 2,3-dimethyl-1,3-butadiene (9a) and 2-methyl-1,3-butadiene (9b) to the cyclobutenes 10a and 10b.[14]



9 10

	ΔH	ΔS
a, R = R' = CH_3	9.6 kcal/mole	-3.6 eu
b, R = CH_3, R' = H	10.6 kcal/mole	-3.9 eu

The authors claim that this is the first example of infrared-laser-induced reactions which are substantially endoentropic and endoenthalpic. By shifting the irradiation frequency, they also reported clean and efficient ring opening of the cyclobutenes. Addition of inert buffer gases, interestingly, resulted in significant yield decreases.

In another publication[15] the same research group reported the trans to cis isomerization of several conjugated and unconjugated alkenes. Their results are shown in Table 1. They found that the highest yields were achieved in cases when the ratio of single-photon absorption cross section of trans to cis is greater than 1.5. Even in cases where the difference in cross section is small, the percent cis isomer was significantly higher than would be predicted from the ratio of cross sections. Based on these observations, they formulated a rate equations model dependent upon absorption cross section, laser fluence, and isomerization rate constants.[14b]

Table 1.

Results of Weitz, et. al.[15] upon IR irradiation of alkenes.

alkene	ν_{ex} cm^{-1}	fluence, J cm^{-2}	steady state, % cis
2-butene	975	4.5	(<95)
2-pentene	949	4.5	88
		6.0	91
crotononitrile	931	3.2	99(<95)
	951	5.5	98(<95)
	978	3.4	99(<95)
1,3-pentadiene	931	2.7	60(63)
	953	2.7	77(80)
		2.9	77(80)
		3.1	78(80)
	982	2.7	(<95)

Hall and Kaldor[17] found that irradiation of cyclopropane gave products, but not relative yields, typical of those formed with thermal excitation. Excitation of the C-H asymmetric stretch at 3.22 μm produced propylene with almost no fragmentation.



Excitation at 9.50 μm resulted in roughly equal yields of propylene and fragmentation products. The role of collisions in this process was investigated by the addition of argon. At 3.22 μm, the effect of collisions with argon was to increase fragmentation yields by opening the upper energy channel (fragmentation) due to intermode vibrational energy distribution. At 9.50 μm, argon tends to favor the lower energy pathway. The authors felt these results were consistent with an excitation that is initially nonstatistical or mode selective.

Finally, it may be possible to effect selective isomerization for those molecules which do not absorb at a convenient frequency by the use of a sensitizer. Nagai and Katayama[18] investigated the photoisomerization of trans- and cis-1,2-dichloroethylene sensitized by SF_6. Irradiation of cis-1,2-dichloroethylene at 10.6 μm in the presence of SF_6 resulted in the formation

of a 2:1 equilibrium mixture of cis- and trans-dichloroethylene. (A comparable mixture is obtained upon heating trans-1,2-dichloroethylene at 400K). No isomerization occurred when cis-dichloroethylene alone was irradiated, since it does not absorb at 10.6 μm. Irradiation of trans-1,2-dichloroethylene in the presence of SF_6 yielded a similar mixture at a rate three times faster than that of the cis irradiation. The yield of fragmentation products was very small.

SUMMARY: The discovery of IR multiphoton excitation has led to applications in the areas of isotope separation, selective chemical reactions, and chemical kinetics; chemical reactions of species generated by this process have been studied using laser induced fluorescence and mass spectrometric detection techniques.[13] While the study of IR MPE-induced isomerization reactions has attracted less interest than dissociation reactions, the high selectivity and quantitative yields of thermodynamically unfavorable isomers obtained in many cases promise to make this area a subject of active investigation in the near future. While only small, relatively uncomplicated molecules and reactions have been investigated so far, IR MPE-induced isomerization has potential for synthetic applications.

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ORGANIC SEMINAR ABSTRACTS

Fall Semester, 1983-84

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Fall Semester, 1983

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NITROSOALKENE AND VINYL-NITROSONIUM CATION CYCLOADDITIONS

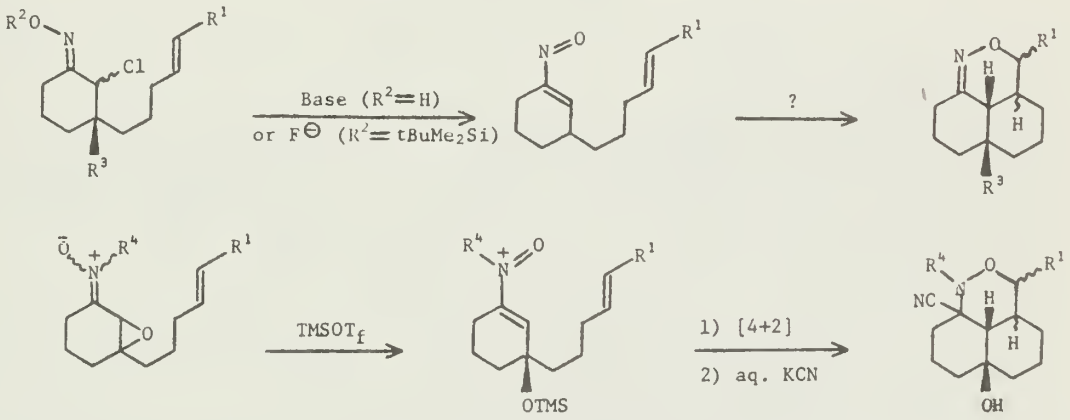
Reported by Michael S. Dappen August 29, 1983

The nitrosoalkene and vinyl-nitrosonium functional groups are not well known.[1] The existence of nitrosoalkenes has been documented by their blue color (due to a long wavelength n-π^* transition, characteristic of nitroso groups[2]), as well as, in a few cases, by isolation[3] and spectroscopic methods.[2] Conjugate addition to nitrosoalkenes, generated by reaction of α-halooximes with base, has been used as a method for nucleophilic functionalization adjacent to a ketone.[4] Intermolecular [4+2] cycloadditions wherein the nitrosoalkene acts as the 4π component have also been reported and are recognized as "inverse electron demand" cycloadditions. These cycloadditions are limited by the need for large excesses of nucleophilic dienophiles and electron withdrawing groups on the nitrosoalkene.[2,5]

Vinyl-nitrosonium cations, generated by reaction of α-chloroaldonitrones with silver tetrafluoroborate[6] or via reaction of α,β-epoxyaldonitrones with trimethylsilyl trifluoromethanesulfonate,[7] undergo extremely facile [4+2] cycloadditions with olefins. The products resulting from these cycloadditions have led to the synthesis of lactones[6] and α- methylene lactones.[7]

We have examined the viability of intramolecular [4+2] cycloadditions using either the nitrosoalkene or the vinyl-nitrosonium moieties as shown in Scheme I.

Scheme I



Cycloadditions of nitrosoalkenes generated from α,β-epoxyoximes[8] were our earliest entry into the field. Attempts using moderately nucleophilic side-chain dienophiles led solely to dimerization. No blue color was observed, leading us to conclude that nitrosoalkenes were generated only in low concentrations. These nitrosoalkenes had other reaction pathways available at low concentrations, such as dimerization in the presence of oximate anions.

Simple model systems of nitrosoalkenes generated from α-chlorooximes were investigated, first, to develop techniques for the preparation of oximes and silyloximes from α-chloroketones, and second, to study the generation of stable nitrosoalkenes from these substrates.[9] Oximes were prepared by reaction of α-chloroketones with hydroxylamine hydrochloride in a buffered methanol or acetic acid solution, depending on the desired oxime geometric isomer and the conformation at the C-Cl bond. Silyloximes were prepared by treatment of α-chloroketones with tert-butyldimethylsilylhy-

droxylamine in the presence of molecular sieves. Generally, nitrosoalkenes were generated smoothly from α- chlorooximes by reaction with triethylamine and from silyloximes by reaction with a fluoride ion source. Nitrosoalkenes underwent side reactions such as dimerization or tautomerization unless the systems were designed to prevent such reactions.

The substrates shown in Scheme I, equation 1 were synthesized by initial preparation of the desired side chain and then, by coupling to 2-cyclohexen-1-one by copper-catalyzed conjugate addition, followed by chlorination of the specific enolate. Oximation or silyloximation followed. Cycloadditions using these substrates were observed only when the appended olefin was an enol ether ($R^1 = OCH_3$).

Intramolecular [4+2] cycloadditions of the vinyl-nitrosonium cation (Scheme I, eq. 2) were also successful. These substrates were prepared by coupling the side chains to 3-ethoxy-2-cyclohexen-1-one, followed by epoxidation and either nitrone or silyloxime formation. Preliminary work has shown that the reactive heterodiene can be generated by treatment of α,β-epoxynitrones with trimethylsilyl trifluoromethanesulfonate or by alkylation of α,β-epoxysilyloximes with methyl trifluoromethanesulfonate. The former method has been shown to be more practical and cycloadditions have been effected in low ($R^4 = CH_3$) to moderate (R^4 = cyclohexyl) yields.

Currently work is being undertaken to vary the side chain length in both types of cycloadditions.

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RECENT SYNTHESES OF 11-OXYGENATED STEROIDS

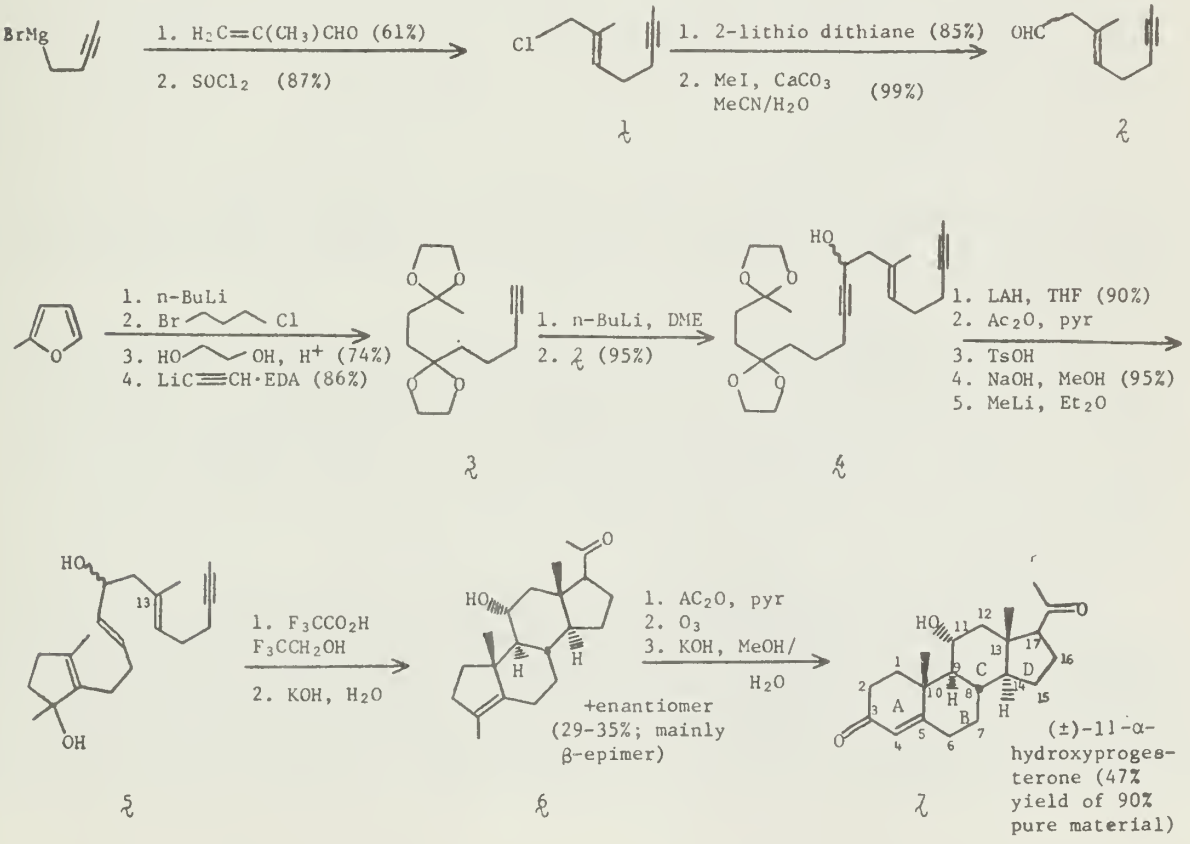
Reported by Karl Habermas September 1, 1983

Many of the steroids secreted by the adrenal cortex contain an oxygen substituent at carbon 11. Glucocorticoids such as cortisol and corticosterone are major regulators of carbohydrate and protein metabolism, while aldosterone functions largely in the control of electrolyte and water balance.[1] Prodigious efforts have been directed toward the construction of these molecules and several total syntheses of 11-oxygenated steroids are celebrated as classic achievements.[2]

A particularly intriguing feature of steroid biosynthesis is the apparently simultaneous creation of seven chiral centers to give lanosterol from the achiral precursor squalene.[3] The cyclization may be viewed as involving trans-anti-parallel addition by incipient carbocationic centers to neighboring π-bonds.[4] Thus the all-trans polyolefin squalene cyclizes to yield a tetracycle with a trans-anti-trans-anti-trans configuration. The process proceeds via a chair-boat-chair-boat folding to provide a cyclized intermediate which undergoes a series of H and methyl 1,2-migrations and final proton loss.[5]

A purely chemical steroid synthesis via polyene cyclization must attain correct product configuration from the thermodynamically favored folding of the precursor, without template action or elaborate 1,2-shifts. These difficulties have been essentially resolved, and 11-oxygenated steroids are also available via the polyene cyclization route,[6] as illustrated below (Scheme I).

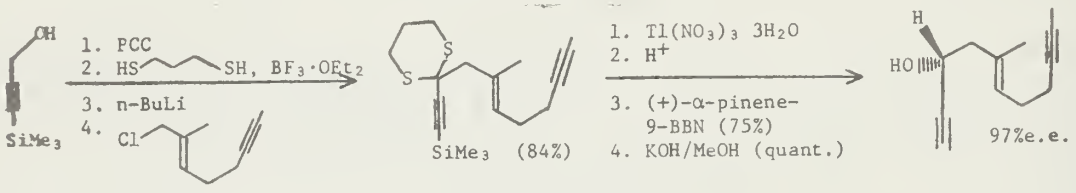
Scheme I.



Addition of 3-pentynylmagnesium bromide to methacrolein, S_Ni' chloridation (→1), reaction with 2-lithiodithiane, and hydrolysis of the thioacetal group gave aldehyde 2. This was combined with the lithium salt of 3, derived in three steps from methylfuran, to provide the diyne 4 in 95% yield.[7] Hydride reduction of the α-hydroxyalkyne, cyclopentenone formation, and methyllithium addition provided the unstable allylic alcohol 5 which was poised for cyclization. Trifluoroacetic acid engendered the cyclopentenyl cation which condensed to form racemic 6. The tetracycle was easily elaborated to (±)-11α-hydroxyprogesterone (7). The efficiency of this synthesis depends upon avoiding too meticulous an imitation of the biosynthetic mechanism. With a methyl group on C-13 in the precursor 5, where, by contrast, it is placed biosynthetically only after a 1,2-shift, Markovnikov addition produces the correct configuration at incipient carbons 8, 9, and 13, obviating the need for template control and substituent rearrangement. Finally, the 5-membered D ring is formed directly by the agency of an acetylenic terminator; i.e., addition to the triple bond occurs preferentially to give a linear, rather than bent, vinyl cation. (The crude product mixture included 4-5% D-homo product and 12% C/D cis fused material).

As cyclization proceeded from the racemic precursor to yield a racemic mixture of a single diastereomer, the chirality in the pro-11 position must be communicated in an enantiospecific condensation. Two 1,3-diaxial interactions in the axial-hydroxyl transition state are absent in the transition state leading to the observed product. The polyene precursor was subsequently obtained in optically active form by resolution, enantioselective addition of lithium trimethylsilylacetylene to an aldehyde catalyzed by (2S, 2'S)-2-(hydroxymethyl)-1-[(1-methylpyrrolidin-2-yl)methyl]pyrrolidine and by asymmetric ketone reduction with Darvon alcohol/LAH[8] or α-pinene/ 9-BBN.[9] The last procedure proved more satisfactory (Scheme II).

Scheme II.



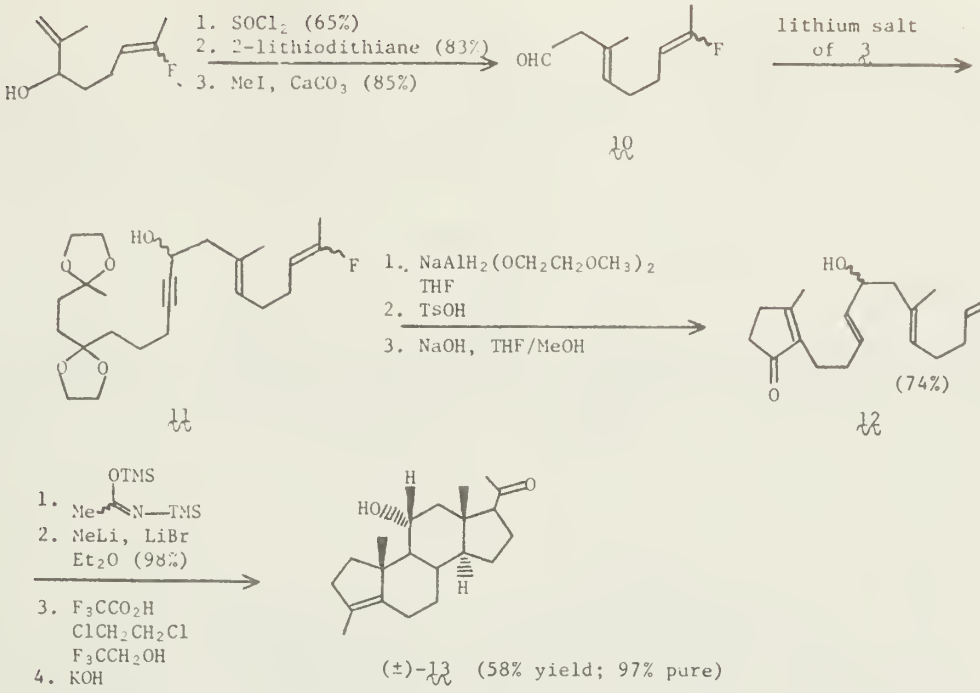
8 9

Borohydride reduction proceeded in excellent yield to produce the diyne 9 with a 97% e.e., the lithium salt of which was combined with the diketal of 1-bromo-4,7-octanedione to form (S)-4.

In a final modification a precursor containing a vinyl fluoride was synthesized (Scheme 3).[10] Protection of the C-11 and careful optimization of reaction conditions markedly improved the yield of cyclized material to 58%. With the vinyl fluoride terminator there were no D-homo side products formed, and the production of C.D cis-fused product was reduced from 12% to 3.3% of the crude product. The racemic product 13 could be converted to 11 α hydroxyprogesterone in two steps.

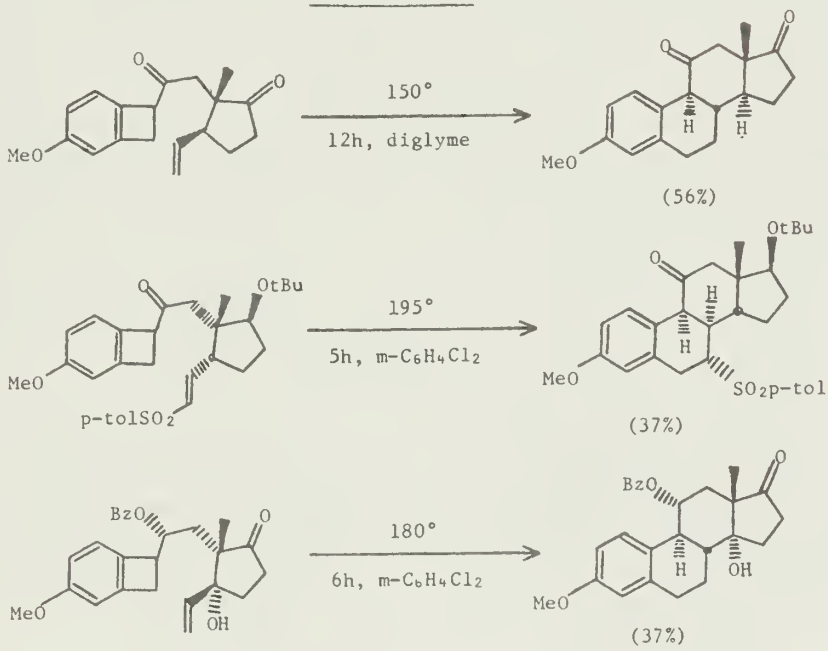
Aromatic steroids, including those with C-11 oxygenation, have been synthesized via [4+2]-intramolecular cycloadditions.[11] Benzocyclobutanes bearing a C-1 chain of five or six atoms with a terminal multiple bond open thermally to give non-aromatic (E)-quino-dimethanes, which can undergo cycloaddition restoring the aromatic ring and simultaneously creating two other rings (Scheme IV).[12,13,14] The high temperature required for opening

Scheme III.



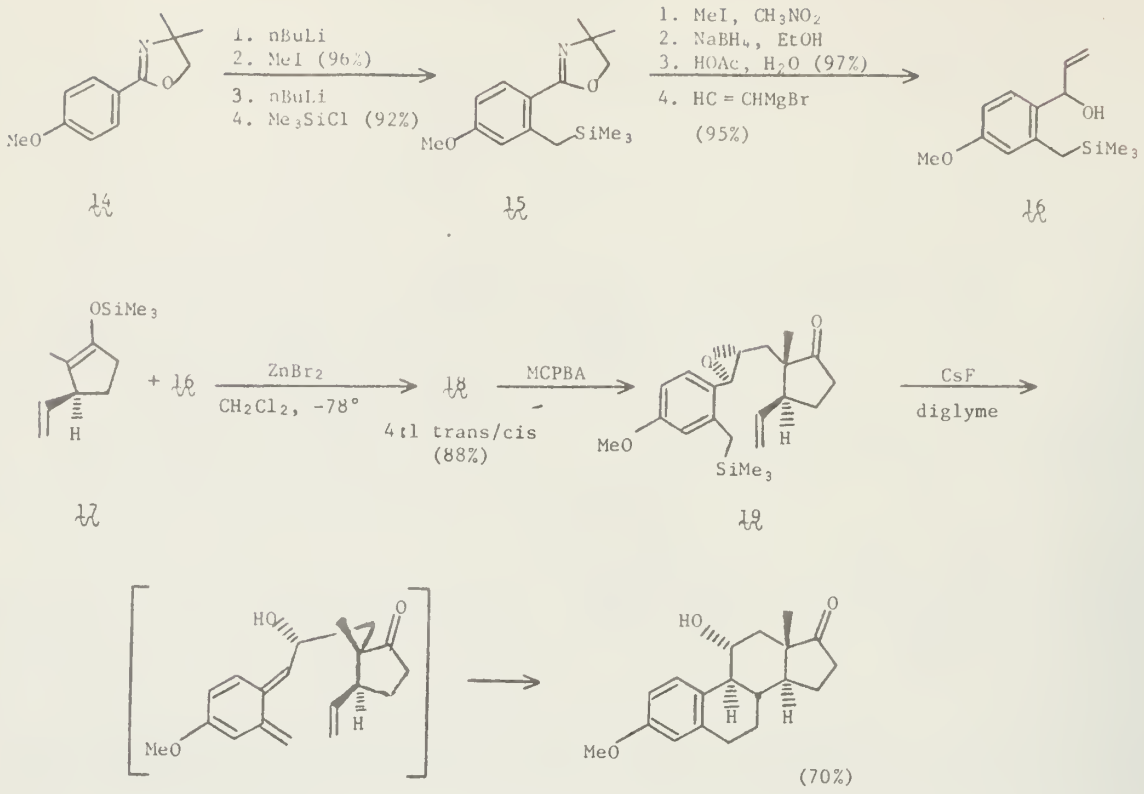
has limited the utility of this approach, particularly for steroids with fairly labile substituents.

Scheme IV.



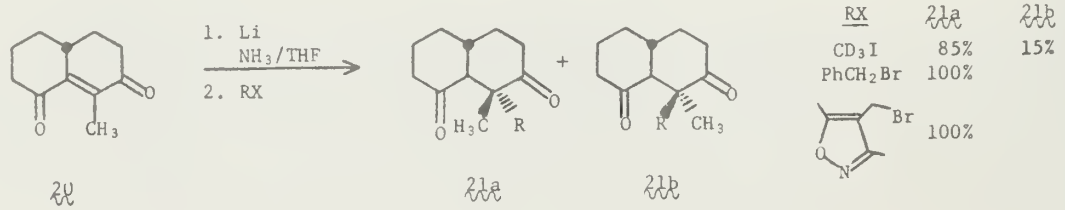
The need for harsh reaction conditions was circumvented in an elegant synthesis of 11α-hydroxy estrone methyl ether (Scheme V).[15] The oxazoline derived from p-methoxy-benzoic acid was alkylated ortho to the heterocycle ring, the benzylic group was substituted with TMSCl, and the directing group was cleaved reductively to give the aldehyde. Grignard addition provided the allylic alcohol 16 in an overall yield of 81% from 14. The trimethylsilyl enol ether 17 was obtained in racemic form by conjugate addition and trapping.

Scheme V.



In a modern variant of the classical Torgov approach $ZnBr_2$ was used to generate the allyl cation of 16 which was captured by the nucleophilic TMS enol ether 17.[16] Reaction occurred cleanly to provide a mixture of diastereomers (trans/cis = 4:1), the predominant product reflecting addition from the less hindered face of the cyclopentenone. MCPBA in buffered CH_2Cl_2 added to the less hindered face of the electron-rich olefin to give a single epoxide. Fluoride catalyzed cleavage of the C-Si bond generated the o-xylylene intermediate at room temperature, furnishing 11α-hydroxyestrone methyl ether in 70% yield.

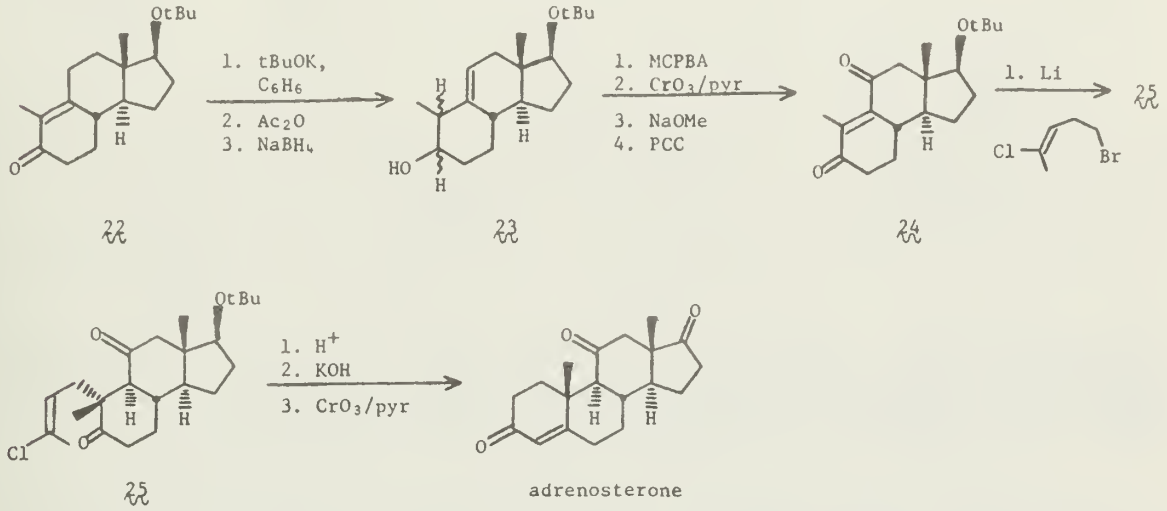
In the first of three recent approaches to 11-keto steroids Stork drew upon his investigations of the reductive alkylation of α,β-unsaturated ketones.[17] In model studies, the enedione 20 was treated with lithium in refluxing ammonia/THF, followed by addition of an alkylating agent.[18] The equatorially alkylated isomer predominated and was the exclusive product with sterically demanding electrophiles. This result is in marked contrast to the firmly precedented axial alkylation of octalone enolates. One interpretation is that crowding between the Me and βO^- substituents is relieved by assuming a boat conformation in the ring to be alkylated, thus exposing the α face. There are, moreover, 1,3-diaxial interactions between H atoms and the approaching electrophile which may hinder axial attack. These interactions are absent for equatorial alkylation.



RX	21a	21b
CD_3I	85%	15%
$PhCH_2Br$	100%	
	100%	

This observation was applied to a stereospecific annelation of the A-ring onto a previously synthesized steroid precursor.[19] The dienal acetate of 22 was reduced to give the homoallylic alcohol, thereby creating the Δ9(11) olefin (steroid numbering)(Scheme 6). Epoxidation and cleavage introduce the C-11 oxygen by a well-established route, followed by allylic oxidation to prepare the enedione system (24). Finally, reductive alkylation with 4-bromo-2-chloro-2-butene, demasking, ring closure, and oxidation completed the synthesis of adrenosterone.

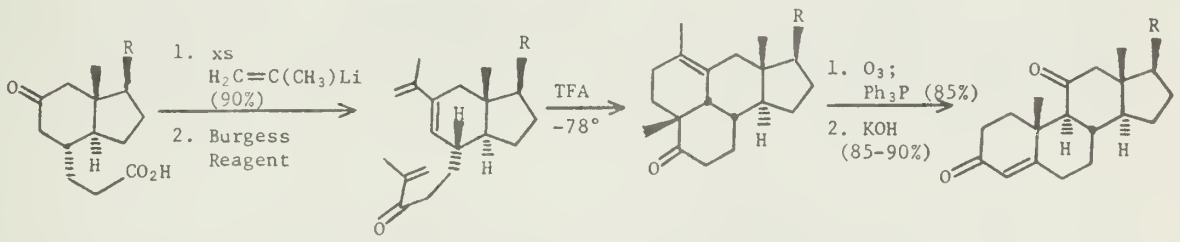
Scheme VI.



22 23 24 25

In a second approach, the steroid skeleton was perceived retrosynthetically as derivable from the ozonolysis product of the tetracyclic Diels-Alder adduct 26b which could be obtained from addition of an isopropenyl and a methacryloyl group (both derived from isopropenyl anion) to a hydrindan-4-propionic acid.[20] Addition of excess isopropenyl lithium to the hydrindanone-propionic acid 26d (prepared, initially, by a cumbersome route), followed by dehydration, gave the cycloaddition precursor 26c (R = $OSiMe_3$) and a small amount of Δ6(7) isomer (hydrindane numbering). Intramolecular Diels-Alder addition was catalyzed by TFA, furnishing the tetracyclic 26b (R = $OSiMe_3$) in 70% yield from the alcohol. Ozonolysis and base-catalyzed epimerization/ring-closure completed the synthesis.

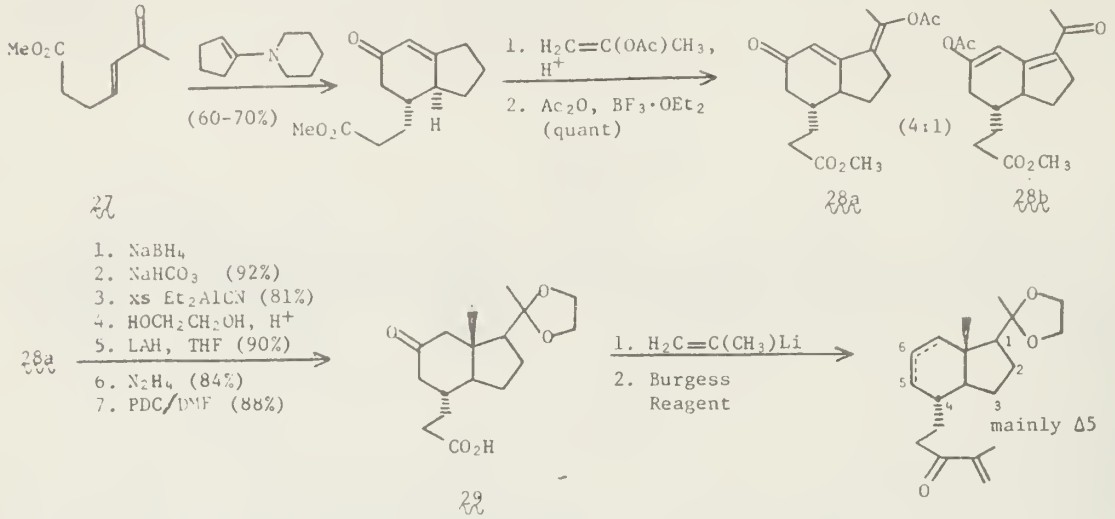
Scheme VII.



26d 26c 26b (70% overall, 94:6 endo/exo) 26a

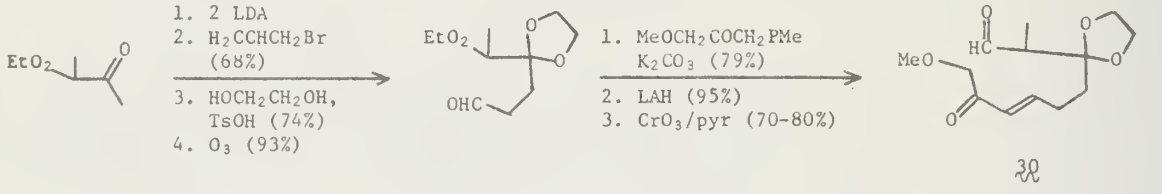
A satisfactory route to the hydrindanepropionic acid was still needed. Preparation of the analogous progesterone precursor (R = $COCH_3$) began with 27 (Scheme 8).[21] Formation of the dienol acetate and reaction with acetic anhydride gave a mixture of enol acetates (28). The minor product could easily be recycled. Reduction of the ketone and deprotection with olefin migration yielded the α,β-unsaturated ketone containing an acetyl group properly positioned for progesterone. Introduction of the angular methyl group was

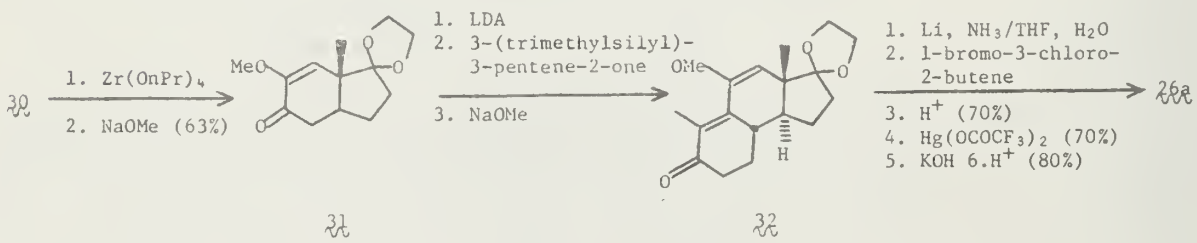
accomplished via conjugate addition of cyanide via Et_2AlCN, which added to render only the desired trans C/D ring product. In sequence, ketone protection, reduction of the nitrile to methyl, and oxidation of the alcohol completed the CD ring precursor, which was subsequently employed in a syn-



thesis of 11-ketoprogesterone. In this instance, there was no exo-adduct detectable. Moreover the incorrect (Δ6) triene could be cyclized to give 26b (R = $COCH_3$) with catalytic $RhCl_3$ in the reaction mixture.

A third approach to 11-keto steroids follows the CD→BCD→ABCD pattern of the first two. Here an internal Michael reaction is employed to create the trans-hydrindane system.[22] Trans product is favored by an amount which varied with the base and appears correlated with the strength of the metallic bond to oxygen. This might be expected since short O-metal bond lengths will bring the two π systems into greater proximity. The anionic charge is disseminated through these π systems and electronic repulsion is minimized if they are perpendicular rather than parallel. This approach was used to synthesize a trans-hydrindane precursor for adrenosterone.[23] The Michael educt 30 was prepared by simple procedures. Zirconium-catalyzed cyclization and dehydration gave the trans-hydrindenone 31 in good yield, introducing the 11-oxygen function as an enol ether. B-ring annelation by established techniques was followed by reductive alkylation, demasking, and ring closure. As before, alkylation proceeded by equatorial attack.

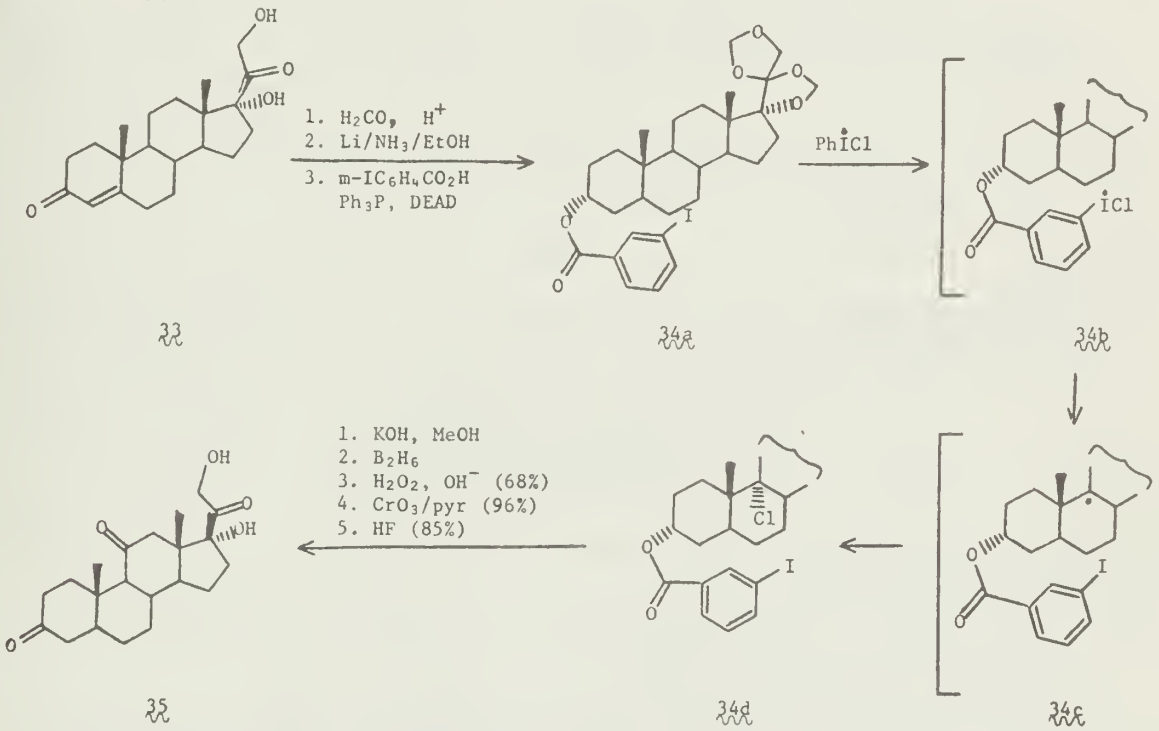




The A ring was unveiled to complete the formation of adrenosterone (26a, R: =O).

Commercial production of corticosteroids is actually accomplished by the oxidative degradation of the relatively inexpensive soybean sterol stigmosterol which provides progesterone in three steps.[24] Microbiological hydroxylation using Rhizopus nigricans gives the 11α-oxygenated product in about 80% yield.[25] Here, the precise geometry of the enzyme-substrate comple achieves the selective functionalization of an unactivated site.

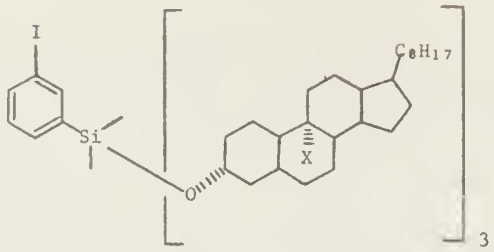
Remote functionalization by means of rigidly attached reagents, which react according to precise geometric control, is another means of delivering 11-oxygenation.[26] Cortexolone (33)[27] was protected as its BMD derivative, the enone was reduced to an equatorial alcohol, and a meta-iodobenzoic acid ester was attached via an esterification sequence which proceeds with inversion of configuration. A small excess of phenyliodide dichloride was added, followed by light or a radical initiator. There are satisfactory indications that the chlorine atom donor transfers Cl· to 34a to generate 34b; the activated aromatic ester then abstracts the C-9 hydrogen via a 13-membered transition state. The rigidity of the steroid skeleton and benzylic ester render this entropically plausible. Since PhICl is selective for abstraction of tertiary hydrogen and geometric constraints preclude attack at C-5 or C-14, the 9-chloro derivative 34d is formed exclusively in high yield. (In the process of chlorination the radical is regenerated). Dehydrohalogenation and saponification give the Δ9(11) olefin, which can be hydroxylated readily at C-11. Jones oxidation and deprotection complete the formation of dihydrocortisone (35), convertible to cortisone acetate by known methods.



33 34a 34b

35 34d 34c

In recent investigation of C-9 chlorination the (m-iodophenyl)-tricholestanyloxysilane 36a was prepared.[28] Addition of SO_2Cl_2 (3.6 equiv.) and catalytic AIBN gave the 9-chloro derivative 36B. Treatment with base gave nearly complete conversion to 9(11) cholesten-3-ol in 75-83% yield. Thus the template functioned catalytically, turning over to chlorinate all three steroids in a given molecule.

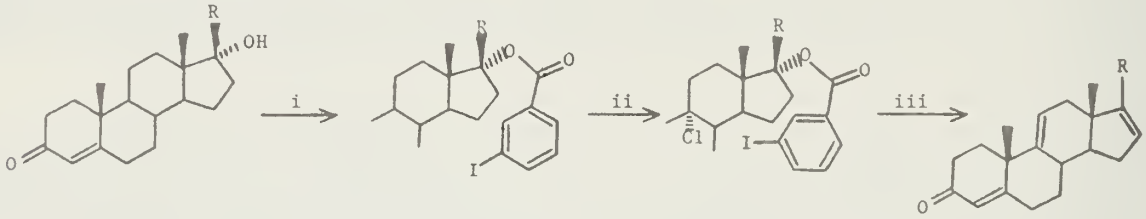


a = H
b = Cl

36

In a remote functionalization from the other end of the steroid, the m-iodobenzoate of 17-epi-testosterone (38a) was synthesized and the radical relay halogenation procedure was accomplished as before.[29] Despite the presence of the sensitive enone functionalty, the 9-chloro derivative (39a) was isolated in 77% yield.

Workers at Schering have refined this approach to provide a useful route to 4,9(11), 16-pregnatriene-3,20-dione (40b),[30] a precursor to several pharmaceutical agents. 17- Hydroxyprogesterone was esterified and the chlorination was effected. Pyrolysis gave the triene 40 in an overall yield of 81% in three steps.



37 b. R = $COCH_3$

38 a. R = H
b. R = $COCH_3$

39

40

(i) (m-C_6H_4CO-)$_2$O
DMAP (95%)

(ii) $PhICl_2$, KOAc, hν

(iii) 250°
(85% from i)

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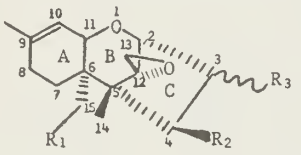
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SYNTHETIC APPROACHES TO TRICHOTHECENES

Reported by Thomas L. Fevig October 3, 1983

The trichothecanes constitute a group of macrocyclic lactones possessing a wide range of biological activity. Produced from Trichothecium roseum and other fungi, they exhibit antibiotic, antifungal, antiviral, and antitumor properties.[1] Common to this group of compounds is the tetracyclic sesquiterpene (trichothecene) nucleus 1.[2,3] The unique structure of this ring system, as well as the promising biological profile of trichothecanes, has prompted many attempts toward the synthesis of trichothecenes.



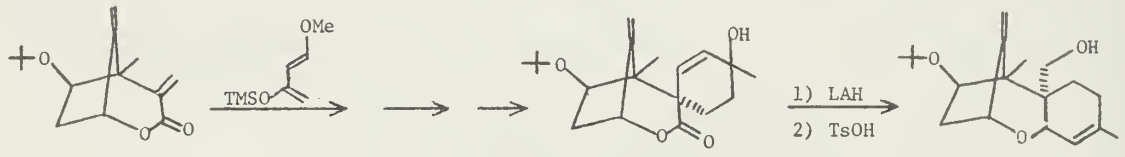
1

R_1	R_2	R_3	
OH	OH	H	verrucarol
OAc	OAc	α-OH	anguidine
H	OAc	H	trichodermin
H	OH	H	trichodermol
OAc	H	α-OAc	calonectrin

Although fairly diverse, the synthetic strategies may be grouped generally within the following categories: 1) annelation of the A ring onto a BC bicyclic precursor (BC → ABC), 2) annelation of the C ring onto an AB ring system (AB → ABC), and 3) biomimetic closure of an appropriate AC ring system to form the B ring (AC → ABC). This report will consider each of these methods.

Several workers have had success with the BC → ABC approach.[1,4,5] The routes are quite similar and are exemplified by Schlessinger's synthesis of ±-verrucarol.[4] Compound 2, in which the B ring is protected as a lactone,

BC → ABC

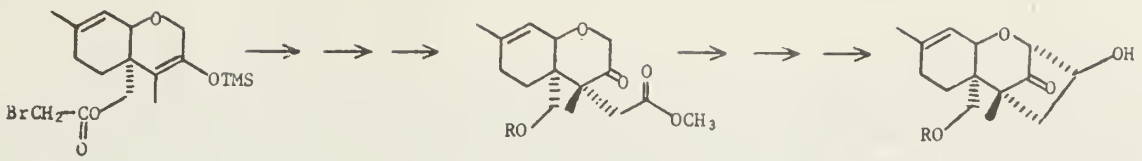


2 3 4

was converted to 3 by a Diels-Alder reaction and subsequent manipulations. Reductive opening of the lactone gave an intermediate diol that underwent an acid-catalyzed S_N2' reaction to form 4, from which verrucarol was prepared in four steps.

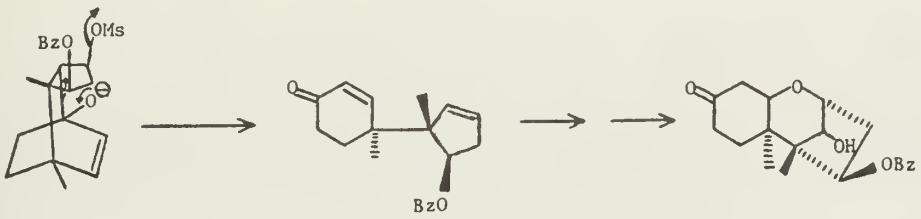
The second general strategy involves formation of the C ring by an intramolecular aldol reaction. Unfortunately, this method is ineffective in the synthesis of C-4—oxygenated compounds.[6] It is, however, a viable approach for the synthesis of C-3—oxygenated trichothecenes, presumably because the requisite enolate is less sterically congested. Kraus and coworkers have prepared ±-calonectrin by this route.[7] Interestingly, their synthesis utilizes the α-hydroxymethyl group at the ultimate C-6 position to control the stereochemistry of the entire aldol sequence:

AB → ABC



The AC → ABC approach has produced some of the most interesting syntheses of 1. A major problem in this route lies in controlling the stereochemistry between the two isolated rings. Still and coworkers have solved this problem using a rigid bicyclo[2.2.2]octene derivative to induce regio- and stereoselectivity. In the key step, fragmentation of 5 unveiled the desired AC ring system 6. Epoxidation on the 5-membered ring and hydrolysis of the epoxide gave a diol which cyclized spontaneously (Michael addition) to give 7. Compound 7 was converted to ±-trichodermol by standard methods.

AC → ABC



5 6 7

In another approach, Trost and coworkers have prepared ±-verrucarol.[9] Stereochemistry was controlled by a Diels-Alder reaction to form the A ring, and again by formation of a hemiketal under thermodynamic conditions. Ring enlargement of the hemiketal gave the ABC ring system.

To summarize, the total synthesis of trichothecenes has been achieved by three basic routes.[10] While the AC → ABC strategy appears to be the most efficient and versatile, there is interesting and useful chemistry in each of the approaches.

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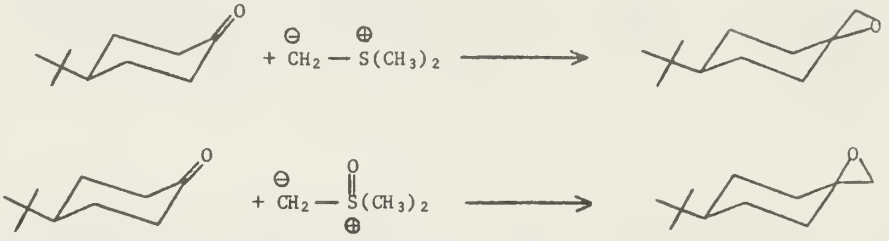
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INTRAMOLECULAR SULFONIUM YLIDE ADDITION TO CARBONYL GROUPS

Reported by Daniel Reno October 13, 1983

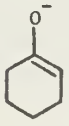
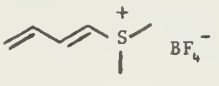
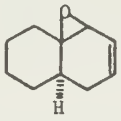
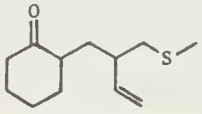
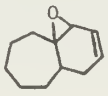
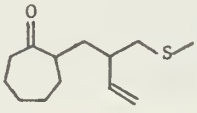
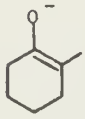
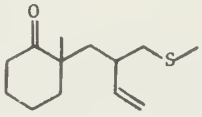
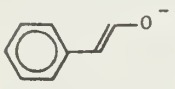
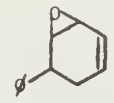
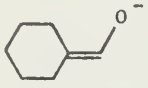
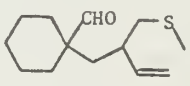
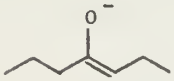
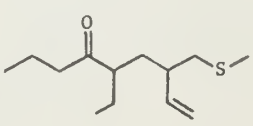
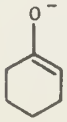
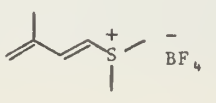
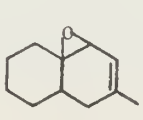
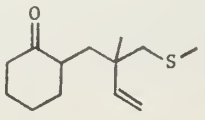
Sulfur ylides react with ketones and aldehydes to form carbon-carbon bonds with subsequent epoxide formation. The addition to the carbonyl often proceeds in a stereoselective manner (Scheme I).[1] The intermolecular version of the ylide addition has received considerable attention and use.[2] The intramolecular version, which has only recently received serious attention,[3-8] is particularly interesting because it can result in ring formation with considerable stereoselectivity.

Scheme I.



Garst and coworkers have reported that 1,3-butadienyl sulfonium salts react with certain enolates to produce dihydroarene oxides (Table 1).[3,6]

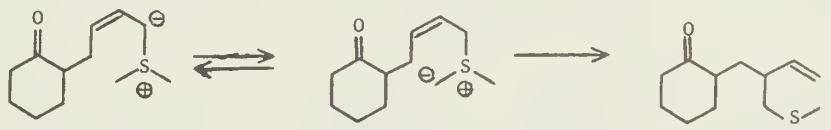
Table 1.

Li^+ Enolate	Sulfonium Salt	Ylide Addition	Ylide Rearrangement
		 (58%)	 (23%)
		 (52%)	 (20%)
		—	 (65%)
		 (45%)	—
		 (48%)	 (31%)
		—	
		 (5%)	 (35%)

The reaction provides cyclized products from the addition of the ylide intermediate that is formed by 1,4 addition of the enolate of cyclic unhindered ketones and aldehydes.

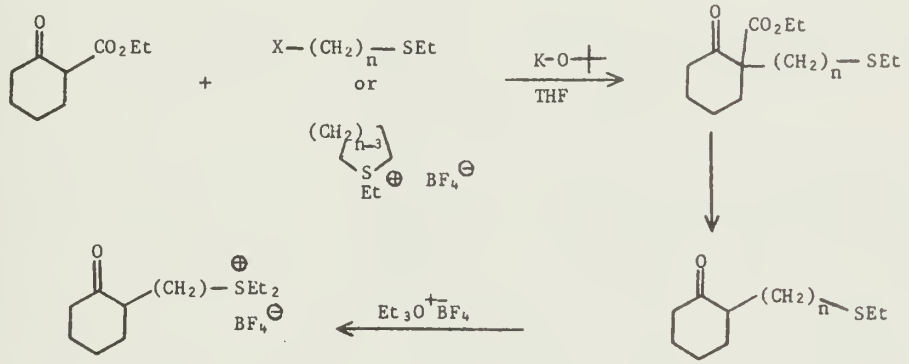
Addition of acyclic or proximally substituted cyclic ketone enolates to the butadienyl sulfonium salts does not result in cyclization. Lack of conformational rigidity of the acyclic ketones and steric interference of the substituted cyclic ketones reduce the rate of addition to the carbonyl so that another process becomes dominant (Scheme II).[6] The [2,3] sigmatropic rearrangement, a well known reaction of allylic sulfur ylides, becomes more facile in these cases.[2] The competing rearrangement process limits the range of ylide cyclization via 1,4 addition of enolates to butadienyl sulfonium salts.

Scheme II.



Oxosulfonium salts provide an alternative method of achieving intramolecular ylide addition to carbonyls.[4,5,7,8] They are readily prepared by the alkylation of β-ketoesters with halosulfides or cyclic sulfonium salts followed by decarboxylation and ethylation of the sulfur (Scheme III). Cyclization is induced by potassium t-butoxide in THF.

Scheme III.



Cyclization of the ylides occurs if ylide addition results in 5- or 6- membered rings. Ring closure proceeds, even with substituted cyclic and acyclic ketones, in moderate to good yields (Table 2). Formation of 7-membered or larger rings is generally not observed because competing intramolecular alkylation of enolates and elimination reactions (Scheme IV) are more facile in such cases.[5,8]

Scheme IV.

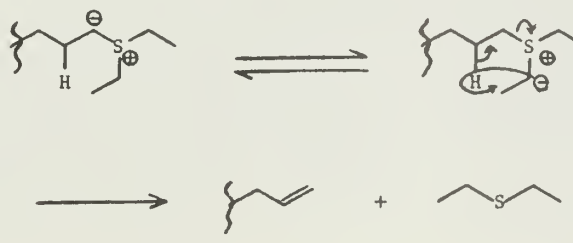
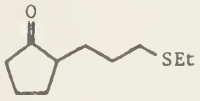
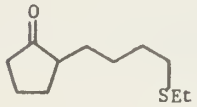
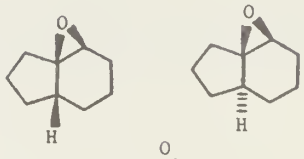
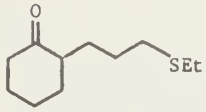
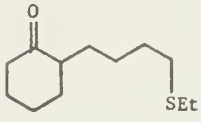
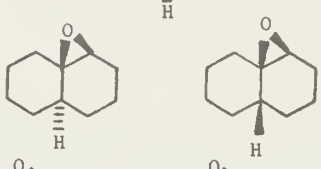
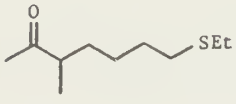
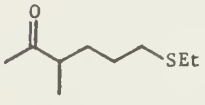
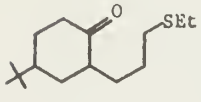
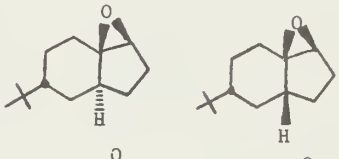
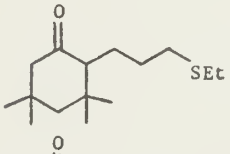
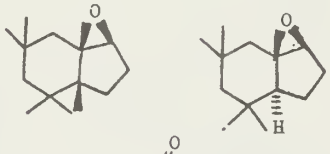
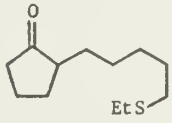
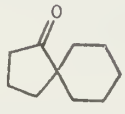
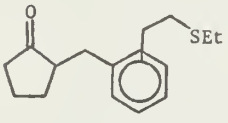
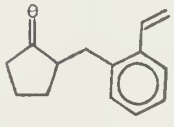


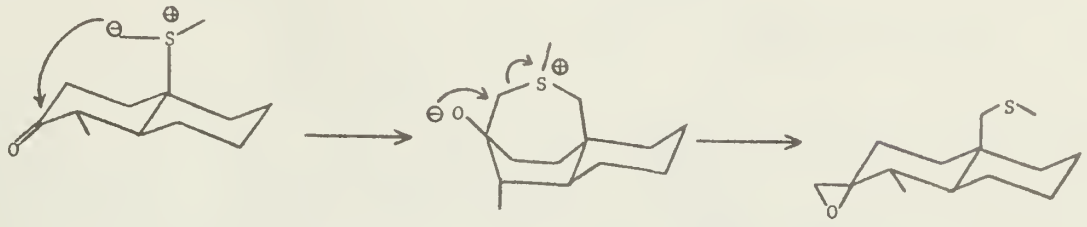
Table 2.

Initial Ketone	Products	Total Yield	Yield ratio
		67%	
		73%	74/26
		99%	
		80%	92/8
		55%	88/12
		80%	21/79
 cis and trans		86%	15/85
		77%	57/43
		34%	
			

Studies of intramolecular Wittig reactions have shown that phosphonium ylides can produce 7-membered rings.[8,9] The sulfur and phosphorus ylides behave differently for several reasons. Phosphonium salts are more acidic than sulfonium salts; therefore, they compete more successfully with enolate formation.[10] Phosphonium salts are also poorer leaving groups which further reduces the probability of alkylation.[11] Elimination is not likely to occur with the triphenylphosphine derived ylides since only one carbon of the system is appreciably acidic. The elimination of competing side reactions thus allows the phosphorus ylide to form 7-membered rings. The addition of a sulfur ylide to a carbonyl by way of a 7-membered ring has been observed; however, it involved alkylidene transfer, not ring formation (Scheme V).[12]

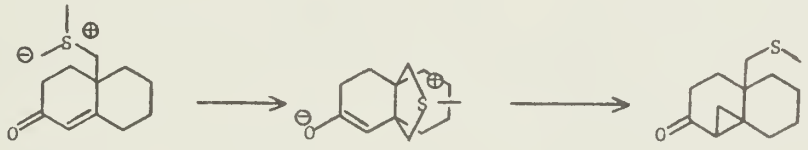
This system is incapable of 1,2 elimination, and alkylation of an enolate would require considerable strain in the transition state. A similar sys-

Scheme V.



tem shows that carbonyl addition is not observed if an alternative reaction can take place (Scheme VI).[13] Conjugate addition, a process not normally observed, becomes more facile than carbonyl addition.

Scheme VI.

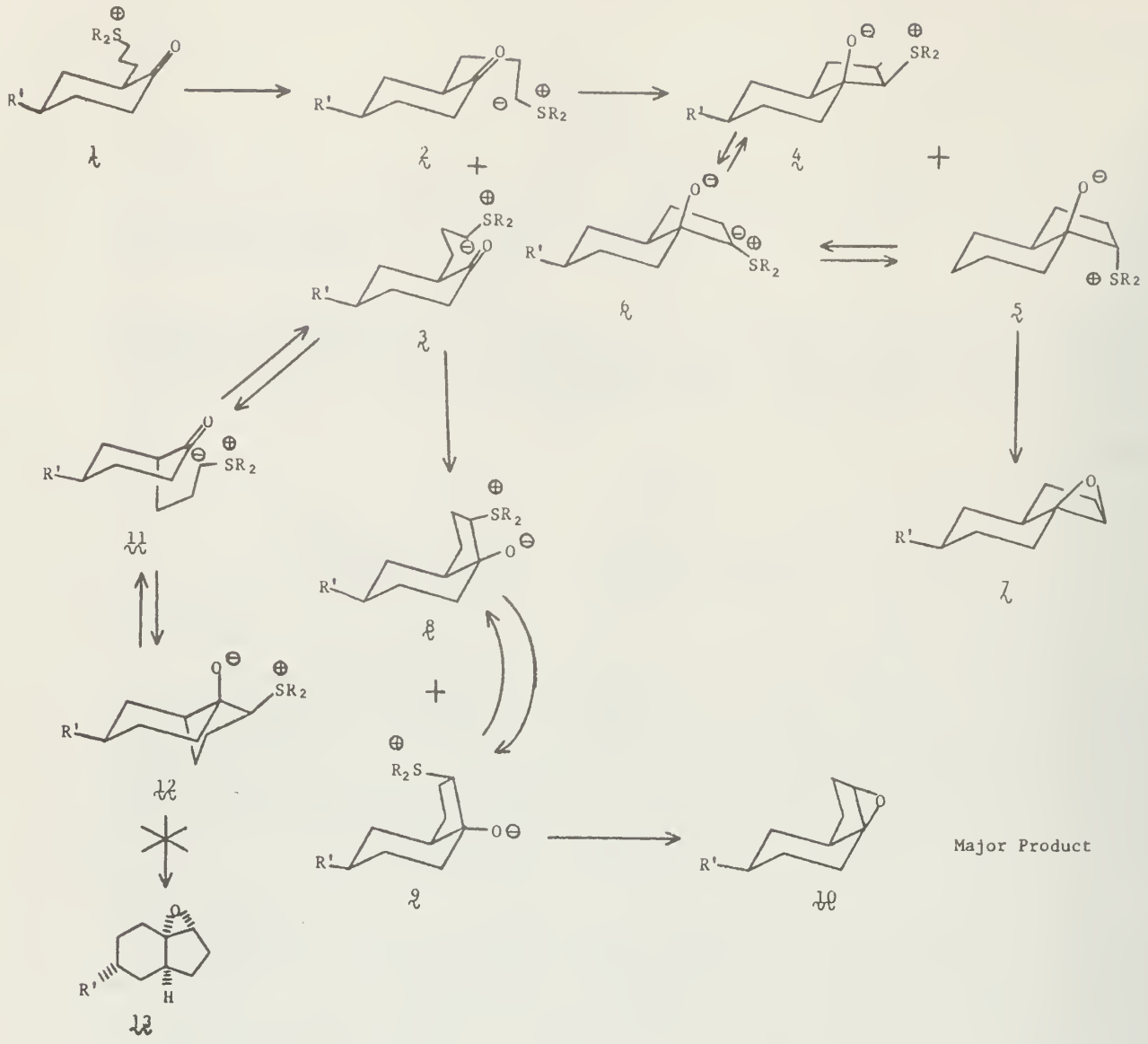


Cyclization of sulfur ylides proceeds with considerable stereoselectivity. The selectivity is rationalized in terms of irreversible ylide addition, conformational constraints, and the trans diaxial arrangement of the betaine required for epoxide formation.[4,5,7,8] The assumption of irreversible ylide addition to the carbonyl is extrapolated from mechanistic studies on intermolecular sulfonium ylide additions which, however, may not necessarily apply to the intramolecular process.[8,14]

The formation of 5-membered rings adjacent to 5- and 6- membered rings indicates that cis addition to the carbonyl is preferred. The cis mode of addition is more facile than the trans because it requires less bond angle distortion to approach the carbonyl carbon (Table 1).[5,8] Steric interactions can reduce the stereoseletivity. Preference for cis addition is diminished in the ylide derived from 2-[3-(phenylthio)propyl]-3,3,5,5-tetramethylcyclohexanone because of the 3,5-diaxial interactions. Ylides derived from cis and trans 4-t-butyl-2-[3-(phenylthio)propyl]cyclohexanone undergo cyclization, and each diastereomer produces the same product distribution, indicating that epimerization is occurring under cyclization conditions. It appears that all products result from the cis epimer.[8] The trans epimer cannot readily attain the proper betaine geometry upon equatorial (cis) addition, and axial addition would require excessive bond angle distortion. Thus, it can be seen that conformational restrictions and betaine geometry are important in controlling stereochemistry.

The study of the t-butylcyclohexane system gives some indication that intramolecular sulfonium ylide addition may not be irreversible. Products resulting from the cis ylide 11b (Scheme VII) are not present. Epoxide 13b is not formed because the betaine precursor cannot easily achieve trans diaxial geometry, therefore, reversibility of ylide addition was postulated, which seems reasonable along this pathway.

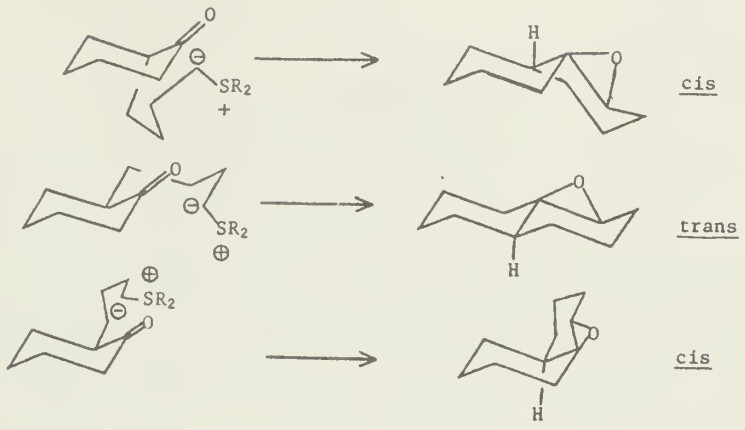
Scheme VII. (a, R' = H; b, R' = t-Bu)



The stereochemistry of ylide addition to form 6-member rings is dependent on the ring system to which it is to be fused. Cis addition to the carbonyl is favored when the adjacent ring is 5-membered. Conformational constraints on addition to the carbonyl carbon appear to be the dominant factor.[5,8] Trans addition to the carbonyl group is favored when the ylide adds to a cyclohexanone derivative. Cis addition by an equatorial ylide to the axial face of the carbonyl and an axial ylide to the equatorial face of the carbonyl experience considerable steric interference by way of two gauche butane carbon-carbon interactions.[5,8] These interactions are absent in the trans addition (Scheme VIII).[5,8]

Intramolecular Darzens condensations constitute an alternative method of ring and epoxide formation. The reaction has received limited investigation.[15,16] The yields are generally lower (22-16%). Stereochemistry is the same in the instances reported as with the intramolecular sulfur ylides. The Darzens method introduces additional functionality such as nitriles, carbonyls and other electron withdrawing groups.

Scheme VIII.



The intramolecular version of diazoalkane addition to carbonyls will produce in some instances rings with epoxides.[17] Substitution in the carbonyl portion facilitates epoxide formation. This method appears to be preferable when the ketone is highly substituted. The drawback to the reaction is that preparation of the diazo system from the parent ketones does not proceed in as high yields as the preparation of the sulfur ylides.

The formation of rings with epoxides by intramolecular Wittig reactions followed by oxidation with MCPBA constitutes yet another method.[8,9] This method exhibits a preference for trans fused systems which makes it a complementary process for 5-membered ring epoxide formation. It is not as stereoselective for the 6-membered ring examples and it does not proceed with as high yields. The ability of the phosphorus ylide to form 7-membered rings, as mentioned above, gives this method one advantage over the sulfur ylide.

In conclusion, the intramolecular addition of sulfonium ylides is a stereoselective process that controls the orientation of ligands at 3 carbons. It is useful as an efficient ring- and epoxide- forming process.

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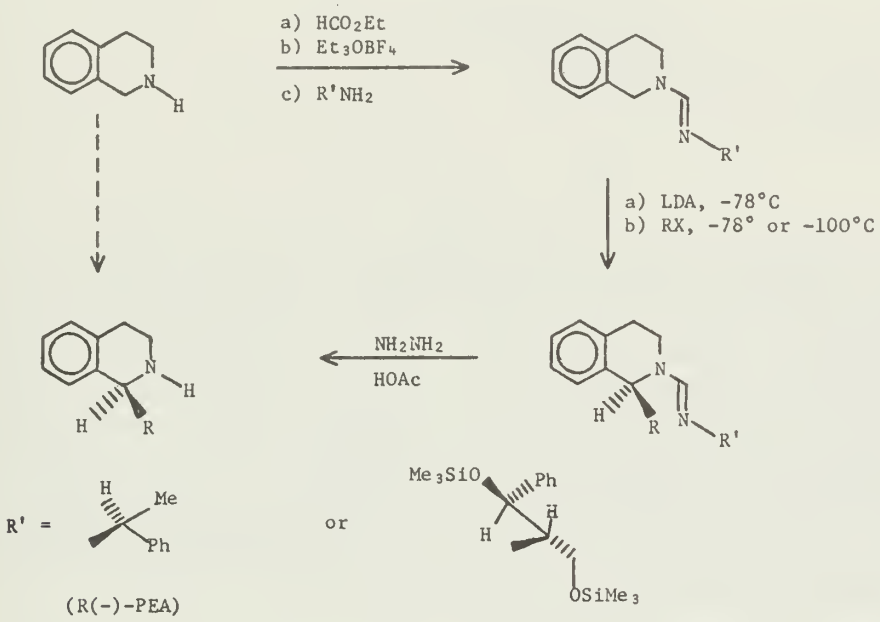
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MECHANISM OF SYN, α'-LITHIATION OF TERTIARY BENZAMIDES

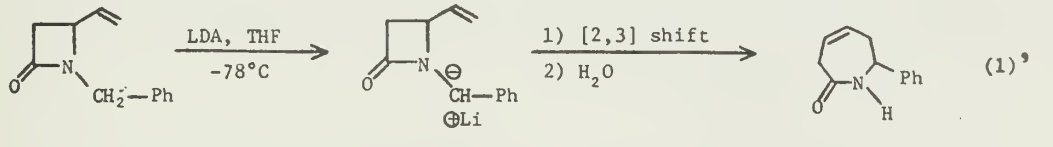
Reported by David R. Hay October 20, 1983

The ability of carbonyl and imine functions to direct lithiation regiospecifically and even stereospecifically to the α' position of amides, esters, thioesters and amidines has been well documented.[1-5] Metalations adjacent to a heteroatom have been developed synthetically[6] by attaching an activating group capable of inducing a formal positive charge on the heteroatom. Such reactions allow the introduction of an electrophile at a carbon that would normally be susceptible to nucleophilic attack, such as hydrolysis of an imine. Removal of the activating group provides an overall conversion of the "Umpolung"[7] type (Scheme I).[5]

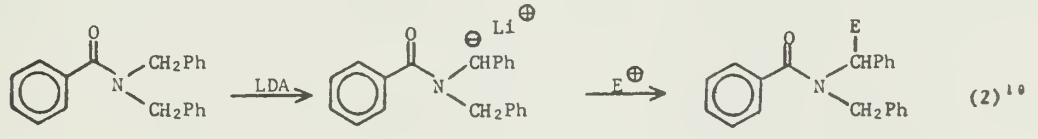
Scheme I.



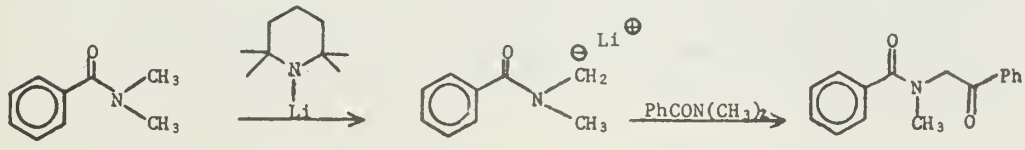
The intermediacy of a carbanion α to nitrogen was first postulated to account for the base-catalyzed substitutions of deuterium at the 2- and 6-positions in 1-methyl-4-pyridone.[8] Later, base-catalyzed reactions of tertiary amides were also proposed to proceed through carbanion intermediates. The general scope of the reaction can be illustrated by the following examples:



(1)[9]

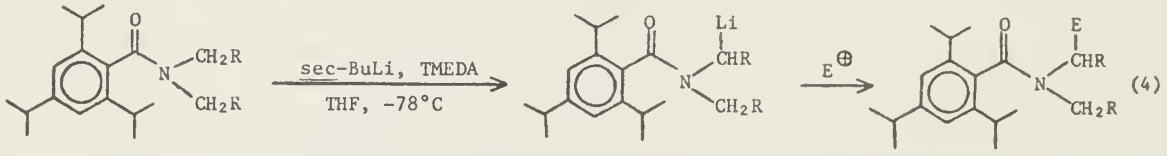


(2)[10]

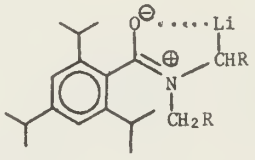


(3)[11]

Studies involving the α'-lithiation of N,N-dialkyl-2,4,6-triisopropylbenzamides and the subsequent reaction with a variety of electrophiles including ketones, aldehydes, alkyl halides and methyl alcohol-d yielded the syn isomer as the observed product (4).[6,12] This result, contrary to ex-



pectation since ab initio SCF calculations predicted the anti isomer should be favored,[2] was interpreted as being indicative of strong binding between the lithium and the amide in a dipole-stabilized carbanion (intermediate 1).[2]



1

The extent to which the nature of the lithium reagent influences the reaction is also important. Studies of organolithium compounds and the mechanisms by which they react with various systems indicate that reactivity is strongly dependent on reagent structure. Alkyllithium reagents exist as aggregates which are in equilibrium with less associated forms.[13] Molecular orbital calculations indicate that such aggregates should be more stable than isolated monomers and should have largely covalent C-Li bonds. The structure and reactivity of organolithium reagents in hydrocarbon solvents can be altered by the introduction of catalytic amounts of alkoxides, amines and ethers. These catalysts cause partial dissociation of the aggregate[20] and increase the polarity of the C-Li bond.[21]

Kinetic studies of phenyllithium dimer with 4,4'-bis(dimethylamino)-benzophenone in toluene-ether indicated the reaction to be first order in phenyllithium.[14] By contrast, the reaction of ketones with methyllithium in diethyl ether was one-fourth order in organolithium and first order in substrate.[15] This latter reaction was interpreted as proceeding through monomeric methyllithium which is in equilibrium with tetrameric methyllithium. The difference in order between these two reactions has been attributed to the difference in solvent polarity. However, the reaction of ketones and esters with sec-butyllithium in cyclohexane was found to proceed through both tetrameric lithium reagent via a complex and monomeric lithium reagent, indicating a more complicated mechanism.[16]

In an investigation of the mechanism of the initial metalation reaction to yield 1, the factors which emerge as influences on the reaction pathway include π delocalization, inductive effects,[17,18] and complexation.[2] In 1983, the first evidence for complex formation was obtained for the reaction of N,N-dimethyl-2,4,6-triisopropylbenzamide with sec-butyllithium.[19] Upon mixing these reagents in an infrared stopped-flow apparatus, a rapidly formed absorbance was detected which slowly disappeared and was replaced by product absorbance. The observed rate constant for formation of the product was inversely related to the alkyllithium concentration. This suggested that equilibrium between tetrameric and monomeric lithium reagent plays an important role in the mechanism.

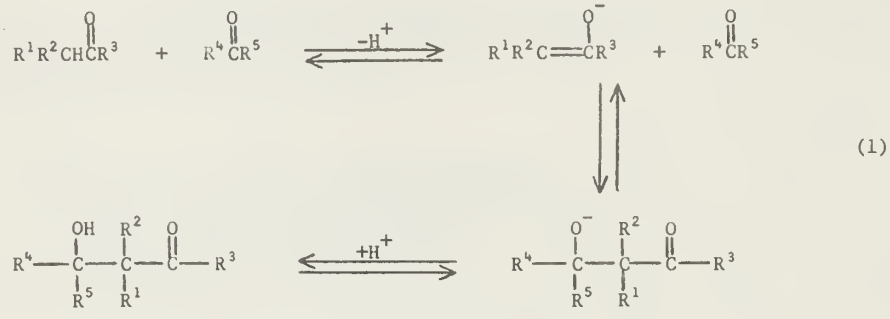
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STEREOSELECTIVE ALDOL REACTIONS VIA ZIRCONIUM, TIN, AND TITANIUM ENOLATES

Written Report by Linda Kostuba October 24, 1983

One of the oldest and most versatile reactions in organic synthesis is the aldol condensation.[1] This venerable process is a well-recognized method for the construction of new carbon-carbon bonds and provides products possessing heteroatoms attached to carbons in a 1,3-relationship and, in general, containing two chiral centers (1). The classical aldol reaction is controlled



(1)

by a series of equilibria which do not necessarily favor the desired adduct.[2] Accordingly, utilization of conventional methods[2] of synthesis has serious limitations, since mixtures of products can result from self- and polycondensations, as well as from regioisomeric enols.

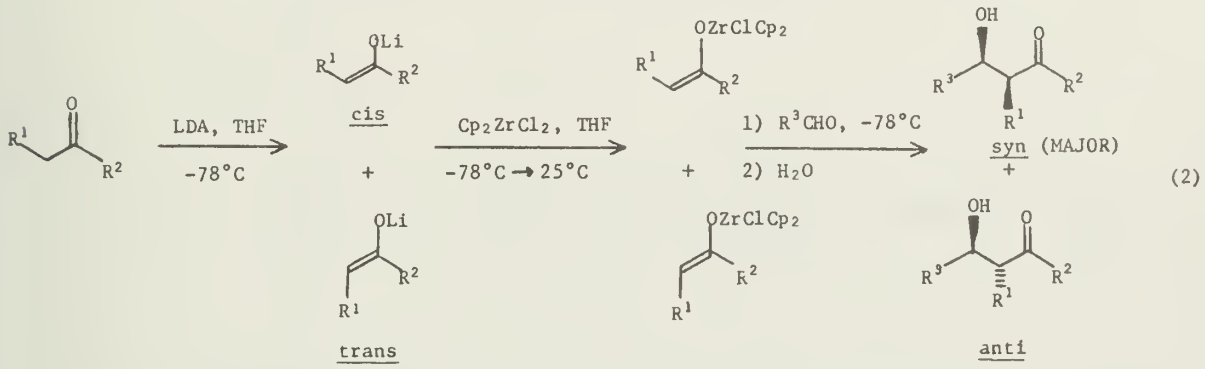
Over the last decade, an intense investigation of the aldol reaction has lead to significant improvements in the classical methodology. Three general approaches to controlling the regiochemistry and stereochemistry of the aldol reaction have been taken. The first general approach to directing the regiochemical outcome of aldol reactions makes use of atoms other than oxygen in one of the fragments, as exemplified by Wittig's use of lithiated Schiff bases as enolate equivalents.[3] Similar regioselective reactions have been performed using lithiated hydrazones[2] and oximes.[2] The second class of aldol reactions employs stabilized enol derivates. Enol silyl ethers[4] (with Lewis acid catalysis[2] or fluoride promotion[5]) and vinyloxyboranes[2,6] have proven to be successful reagents for regioselective, and in some cases stereoselective, synthesis of aldol-type products. The remaining class of aldol reactions utilizes preformed enolate anions with various metal counterions. Early examples include the use of halomagnesium,[7] bromozinc,[8] and aluminum[9] enolates, but certainly the most extensively studied enolates of this type are the lithium enolates.[2,10] These lithium enolates, along with the recently developed boron enolates,[2,6] are among the most successful for attaining regio- and stereochemically controlled aldol condensations.[2] The growing interest of organic chemists in utilizing transition metals in synthesis has had a profound effect in the field of aldol chemistry, especially in this third category. While many types of transition-metal enolates have been used in the aldol reaction, we will focus only on recent advances in the use of zirconium, tin, and titanium enolates in effecting selective aldol reactions.

Zirconium Enolates

It is now well established[2] that for kinetically controlled aldol reactions, incorporation of appropriate steric control elements into the carbon skeleton of enolates of Group I, II, and III metals results in diastereoselective aldol condensations. In such cases, one obtains mainly syn aldol products from cis enolates and anti aldol products from trans

enolates.[11] Alternatively, the steric control elements may be incorporated primarily on the metal center providing altered diastereoselectivity in the aldol reaction.

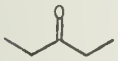
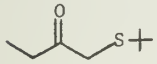
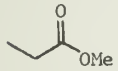
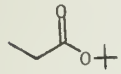
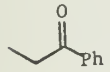
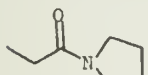
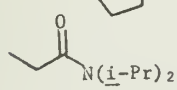
To determine the role sterically demanding metal centers play in aldol stereoregulation of kinetically controlled reactions, Evans[12] has studied biscyclopentadienylchlorozirconium enolates. These zirconium enolates, prepared from the corresponding lithium enolates by ligand exchange with Cp_2ZrCl_2 (Cp = η^5-cyclopentadienyl), react with aldehydes to yield predominantly syn-β-hydroxyketones, -esters, and -amides.[12] The striking feature of this aldol reaction is the syn diastereoselection from both cis and trans enolates (2). A comparison of β-hydroxyketones, -esters, and -amides ob-



(2)

tained by reaction of lithium enolates[13] and zirconium enolates with benzaldehyde is illustrated in Table I.[12,14] Also studied[14] were cyclopentanone

Table I

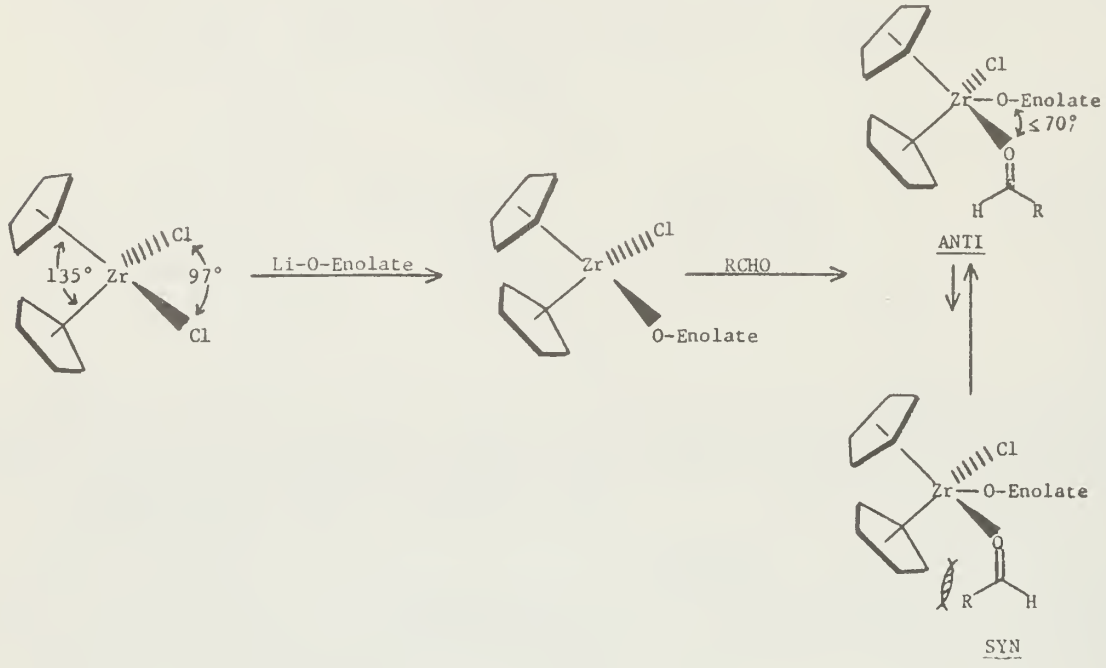
substrate	enolate ratio	product ratios		
		Li	Zr	
	cis:trans	syn:anti	syn:anti	(% yield)
	14:86	30:70	88:12	(70)
	10:90	63:37	93:7	(70)
	5:95	52:48	87:13	(80)
	5:95	37:63	72:28	--
	>98:2	82:18	90:10	(62)
	>95:5	60:40	95:5	(80)
	81:19	61:39	>98:2	(87)

and cyclohexanone zirconium enolates that have a fixed trans geometry yet give high aldol yields comprised of 65-75% syn products.

Two models are proposed to rationalize this directed relationship between enolate geometry and aldol configuration: one, of Yamamoto, an acyclic transition state as lowest in energy due to the added steric hinderance at

the metal center;[14] the other, of Evans, a pericyclic transition state, in which trans zirconium enolates react preferentially via a psuedo-boat conformation and cis zirconium enolates proceed via a psuedo-chair conformation. The vacant ligation site in 16-electron zirconocenes such as Cp_2ZrCl_2, according to theory,[15a] lies in Cl-Zr-Cl plane, and the bond angle between the chlorine ligands is 97°.[15b] Therefore, the corresponding 18-electron complexes are thought to have an even smaller bond angle ($\leq 70°$)[15c] between ligands, (Scheme I). Also, on steric grounds the anti aldehyde complex

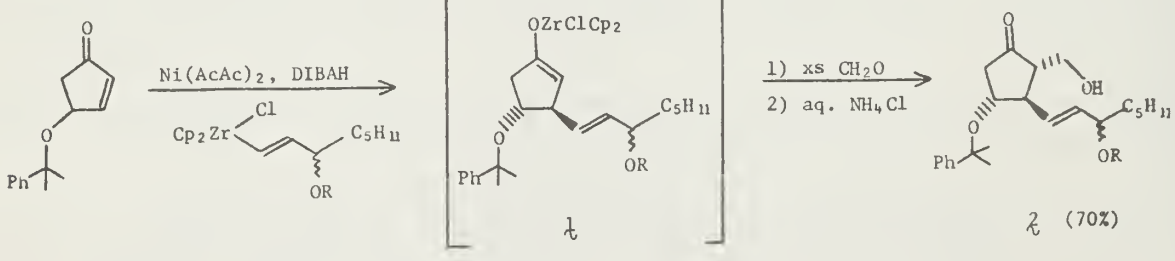
Scheme I



should be favored over the syn aldehyde complex (Note: syn and anti are not being used here to denote product stereochemistry).[2b] Although this rationalization via a pericyclic transition state is clearly speculative, a supportive preliminary report[16] indicates that more hindered bent-sandwich complexes [(pentamethylcyclopentadienyl)zirconium enolates] fail to take part in aldol condensations.

Isolable zirconium enolates can be obtained via nickel-catalyzed conjugate addition of alkenyl zirconium species to α,β-unsaturated ketones.[17] Studying the application of this conjugate addition reaction to the synthesis of prostaglandin derivatives, Schwartz[18] obtained α-(hydroxymethyl)cycloalkanones (2) upon trapping of the zirconium enolates 1 (R = $Si(CH_3)_2$t-Bu or CH_2OCH_2Ph) generated in situ with formaldehyde (Scheme II). Zirconium

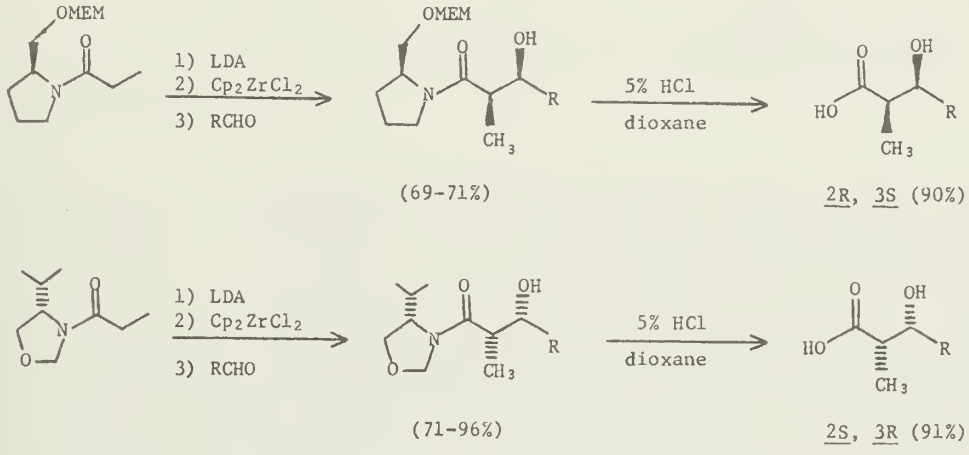
Scheme II



enolates were also useful in the synthesis of other natural products such as Rifamycin S[19a] and some β-lactam systems.[19b]

Finally, enantioselective aldol condensations have been developed utilizing optically active amide zirconium enolates.[20a] Use of chiral auxiliaries[20] shown in Scheme III (R = n-Bu, i-Pr, Ph) provide excellent

Scheme III

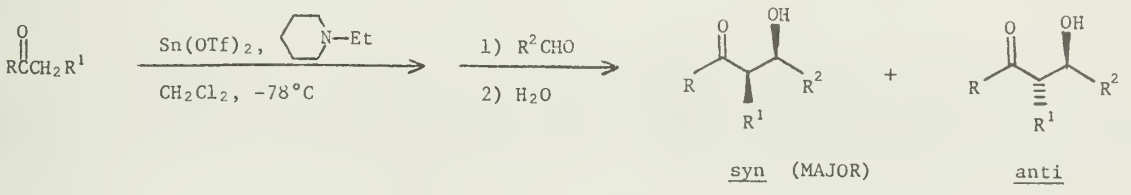


levels of asymmetric induction in the aldol process, whereas the corresponding lithium enolates give aldol reactions that are nearly stereorandom. The high levels of syn diastereoselection (96-98%) and the diastereofacial selection within the syn product manifold (50-200:1) is quite impressive. The resultant β-hydroxyamides readily undergo mild acid-catalyzed hydrolysis to the carboxylic acids via N → O acyl transfer without loss of stereochemistry.[20a]

Tin Enolates

Mukaiyama and Iwasawa[21] found that ketones (R = Ph, Et, i-Pr; R^1 = Me and R, R^1 = $-CH_2(CH_2)_3CH_2-$, Scheme IV) react with stannous trifluoromethane sulfonate in the presence of a tertiary amine to produce divalent tin enolates. These react with a variety of aldehydes (R^2 = Ph, i-Pr, n-Pr) to give the corresponding aldol products in high yield (71-86%) with good to excellent syn selectivity (86 to >95%). An enantioselective aldol process is achieved

Scheme IV

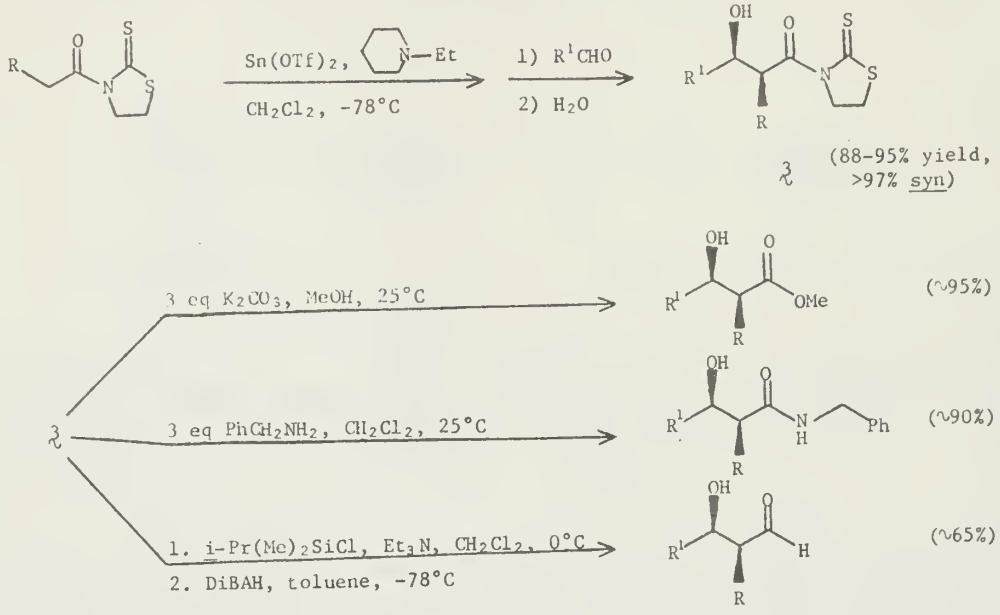


by the addition of optically pure (S)-proline-derived chiral diamines to the divalent tin enolates generated in situ.[22] It is supposed that this enantioselectivity (up to 90% e.e.) results from chelation of the bidentate diamine to the vacant tin d orbitals to form a rigid five-membered ring, thus imposing a stereobias on the transition state for the aldol reaction.[22]

In related studies, the syn diastereomers of β-hydroxyaldehydes, -esters, -amides were obtained selectively via stannous-triflate mediated

aldol condensations[23a] by reaction of the carbonyl equivalent, 3-acylthiazolidine-2-thione (R = H, Me, $PhCH_2$),[23b] with a variety of aldehydes (R^1 = Ph, PhC_2H_5, i-Pr). Conversion of the aldol product (3) to various β-hydroxy carbonyl compounds is shown in Scheme V.[23] Furthermore, the

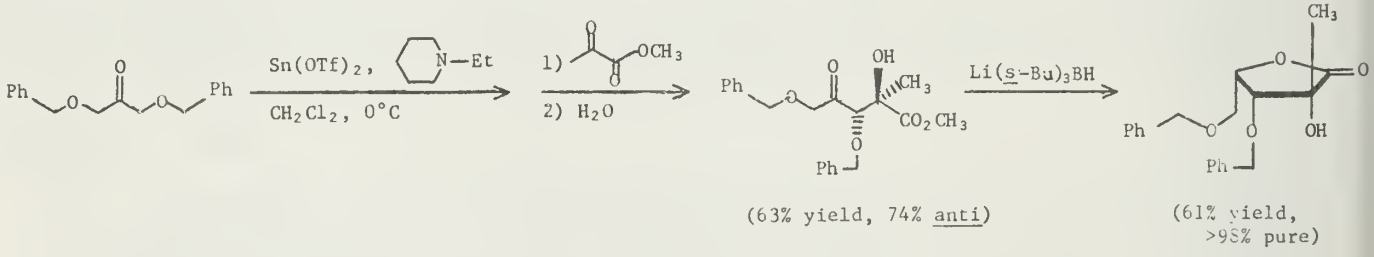
Scheme V



addition of (S)-1-methyl-2[(piperidin-1-yl)-methyl]pyrrolidine (a chiral diamine derived from (S)-proline) to the preformed divalent enolate in this reaction results in optically active aldols (up to 90% e.e.).[24]

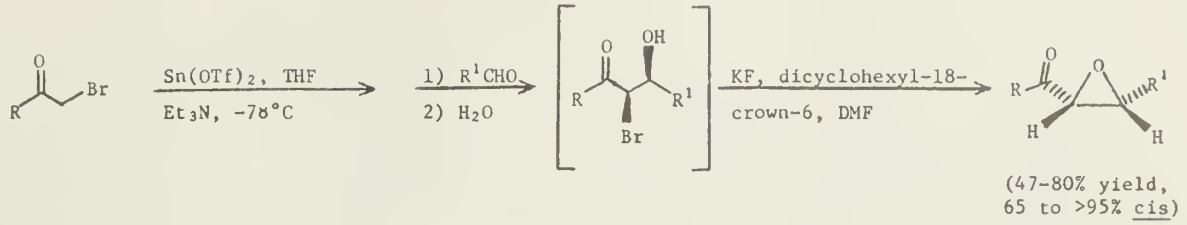
During the study of the stannous-triflate mediated cross-aldol reaction it was found that under certain conditions methyl ketones afford self-condensed aldol products in high yields.[21] Further investigation of this self-condensation reaction demonstrated its utility for the cross-coupling of ketones. Where diastereoselectivity was observed, generally the anti aldols were obtained.[25] This directed aldol reaction was utilized in the construction of a branched-chain sugar backbone, providing a simple two-step route to the saccharinic acid γ-lactone, 2-C-methyl-DL-lyxonolactone (Scheme VI).[26]

Scheme VI



A modification of this divalent tin-mediated aldol reaction has been applied to the stereoselective synthesis of cis-α,β-epoxyketones from α-bromoketones (R = Me, Ph, t-Bu) and aldehydes (R^1 = Ph, PhC_2H_4, i-Pr) (Scheme VII).[27] Other divalent tin enolates which participate in aldol

Scheme VII



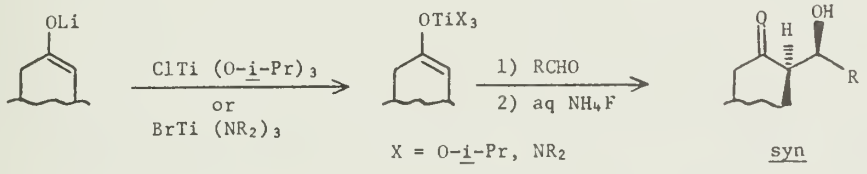
or aldol-like reactions are generated by the treatment of activated metallic tin species with α-bromoketones,[28a] α-bromoesters,[28b] and α-dicarbonyl-compounds.[28c]

Triorganostannyl enolates also have been reported to participate in aldol reactions, but the results have been somewhat conflicting. Yamamoto[29a] reported that syn isomers result from the reaction of aldehydes with triphenyltin enolates generated in situ under kinetic control, whereas Stille[29b] obtained anti isomers under kinetic control from the reaction of isolated trimethyl-, triethyl-, and tributyltin enolates with aldehydes. Although preliminary spectroscopic studies[29b,c] indicate that the O-stannyl enolates do initially produce anti products at low temperature, further examination of the mechanistic aspects of these reactions is required before any clear interpretation can be made.

Titanium Enolates

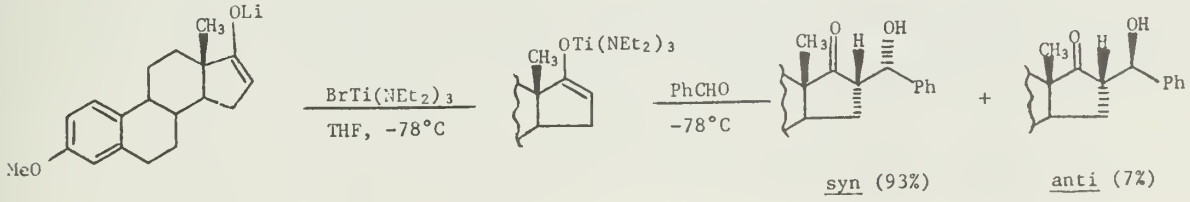
Titanium enolates are readily prepared by trapping the corresponding litnium enolates with chlorotitanium triisopropoxide [ClTi(O-i-Pr)$_3$] or bromotitanium tris(dialkylamide)[BrTi(NR$_2$)$_3$, R = Me or Et).[30,31] These titanium enolates react with aldehydes to afford syn aldol adducts with high diastereoselectivity.[31] When acyclic ketones (cyclopentanone, cyclohexanone, and cycloheptanone) are utilized the conversion is high (>70% isolated), and the syn selectivity is maintained (85-97%) (Scheme VIII).

Scheme VIII



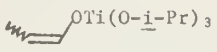
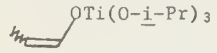
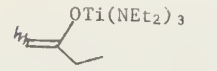
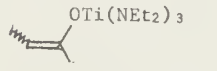
An application of a titanium tris(diethylamide)enolate to synthesis is shown in Scheme IX. O-Methyl estrone, after conversion to the titanium enolate, undergoes a syn selective aldol condensation trans to the angular methyl group, providing primarily one of the four possible diastereomers.[32]

Scheme IX



Also, acyclic ketones, once converted into titanium enolates by the same methodology, react with aldehydes to yield predominately syn aldol adducts irrespective of the geometry of the enolate (Table II).[31a] It was noted, however, that in a few cases the diastereoselectivity was reversed.

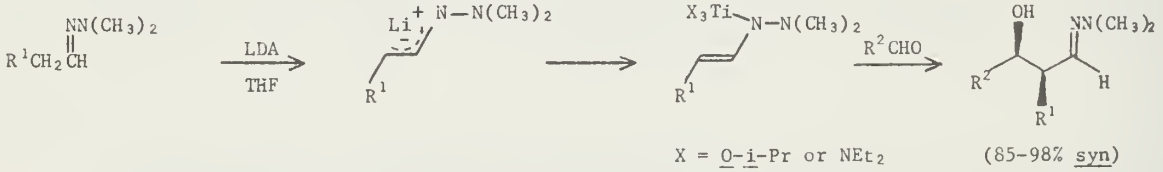
Table II

enolate type	enolate cis:trans	aldehyde	product ratio syn:anti
	36:64	PhCHO	89:11
	92:8	+CHO	81:19
	36:64	PhCHO	76:24
	5:95	PhCHO	74:26

The preparation of trichlorotitanium enolates from enol silyl ethers and $TiCl_4$ has been reported,[33a] and most are stable for hours to days under nitrogen at 20-30°C. Reaction of these trichlorotitanium enolates with aldehydes at -70°C leads to rapid formation of the aldol product in generally high yield and with high syn diastereoselectivity.[33b] Aldol reactions involving titanium enolates are believed to proceed via a pericyclic transition state, the conformation of which depends upon enolate geometry, the substituents, and the nature of the aldehyde,[30,31,33] much as in the case of zirconium enolates.

Titanium enolate equivalents useful in aldol-like reactions developed by Reetz et al.[34] are titanated hydrazones derived from aldehydes. Titanation of lithiated aldehyde-hydrazones (R^1 = Me, Ph, i-Pr, Scheme X) by chlorotitanium triisopropoxide or bromotitanium tris(diethylamide) leads to reagents which react syn selectively with aldehydes (R^2 = Ph, p-$NO_2C_6H_4$, Me, i-Pr, t-Bu) in acceptable yields (40-95%).[34] This syn selectivity is also

Scheme X



X = O-i-Pr or NEt_2 (85-98% syn)

observed with titaniated ketone-hydrazones and Schiff bases; however, the resulting aldol-like products from the Schiff bases are somewhat unstable and isomerize slowly to the anti adducts.[34]

Clearly, although the use of these metals in the aldol reaction is in an early stage of development, the factors governing stereoselection are being elucidated and hold promise of efficiency and stereochemical predictability in aldol condensations.

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11. In describing enolates in this abstract, cis and trans refer to the relationship between the enolate oxygen and the alkyl group attached to the adjacent carbon of the double bond. The relative configuration of the aldol adducts is determined by drawing the aldol in an extended (zigzag) manner. When the β-hydroxy group and the α-alkyl group are on the same side of the plane defined by the main chain, the product is designated syn, and when on opposite sides of the plane, the product is called anti. All products drawn in this abstract are racemates unless otherwise indicated. Other systems of nomenclature are sometimes used.[16]
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THE USE OF CRYPTANDS IN ORGANIC SYNTHESIS

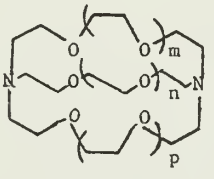
Reported by Gary L. Clauson October 27, 1983

The cryptands, first synthesized in 1969 by Lehn and coworkers,[1] are a class of macrobicyclic compounds possessing a "cave-like" interior. Like their relatives, the coronands, the cryptands are capable of complexing metal cations strongly; however, the strength of such complexes (cryptates[2]) is 10^3- 10^5 times greater than that of the coronates. Thus, cryptands are generally superior at dissolving metal salts in both aqueous and non-aqueous media (e.g. $BaSO_4$[K_{sp} = 10^{-10}] in water, $KMnO_4$ in benzene), and they greatly enhance the solubility of the alkali metals themselves in amine and ether solvents. Such metal solutions are ionic, containing cryptated metal cations and solvated electrons and/or alkali metal anions,[3] depending on the stoichiometry used; some electride and alkalide salts have been isolated.[4]

The cryptands and their cryptates, although widely used in analytical chemistry,[5] have seen only limited use in organic synthesis. This report will focus on the following: (1) Phase transfer catalysis, (2) Anion activation, (3) Superbasicity, and (4) Miscellaneous aspects, which include general improvement in yields or reduction of reaction times, changes in regio- or stereoselectivity, and reactions of potential use. First, however, some background material on cryptands is in order.

Nomenclature and Synthesis

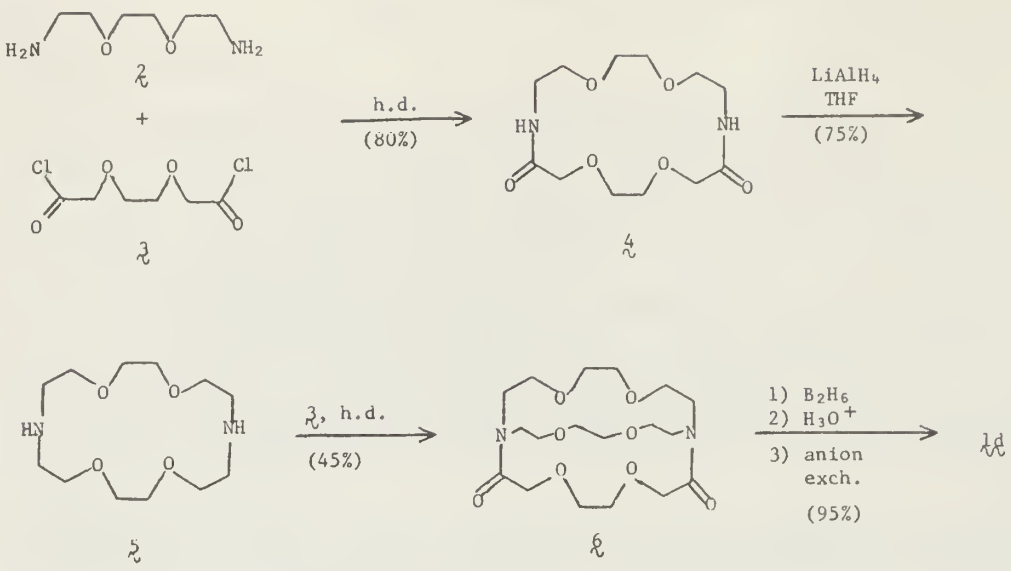
The general structure for a cryptand, 1, is based on Lehn's original compounds; however, the term cryptand today is used to describe a wide variety of macrobicyclic heterocycles.[6] For the sake of brevity, the abbreviation Cmnp[7] will be used in place of the somewhat cumbersome IUPAC name (for example, C222 in place of 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo-[8.8.8]hexacosane, where the 2's refer to the numbers of oxygens in the bridges). This type of cryptand is synthesized generally by the sequence[1,7b] shown in Scheme I for C222. Recently, a "one-pot" template method has been developed[8] which eliminates the need for high dilution conditions and gives C222 (1d) in 21% overall yield, comparable to the overall yield realized in Scheme I. Many of the cryptands (1 and others) are now available as specialty chemicals, although they are somewhat expensive; however, their use in what are usually catalytic amounts and their ability to be recycled efficiently[9] help to reduce their cost per reaction. Another cost-saving measure is the use of polymer-supported cryptands for those reactions amenable to phase transfer catalysis.



1

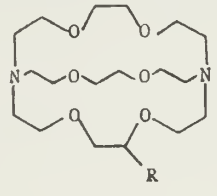
1a	m=n=p=o	C111
b	m=n=o, p=1	C211
c	m=o, n=p=1	C221
d	m=n=p=1	C222

Scheme I



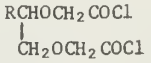
Phase Transfer Catalysis

The cryptands 1, since they are soluble in both water and organic solvents, would seem to be ideally suited for use in phase transfer catalysis (PTC). However, they are too water soluble and are not very efficient in transferring the reactive species into the organic phase. A great improvement in efficiency, as evidenced by a shorter time and/or lower temperature requirement, has been realized when a lipophilic side chain was attached to the molecule, as in 7.[10] These were synthesized from the acid chlorides 8 and C22(5) and have been used in a number of phase transfer catalyzed reac-



7

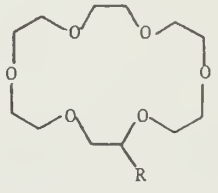
7a R = n-$C_{10}H_{21}$
b R = n-$C_{11}H_{23}$
c R = n-$C_{14}H_{29}$
d R = n-$C_{20}H_{41}$
e R = $HOCH_2$-
f R = $H_2N(CH_2)_9$-
g R = n-$C_{16}H_{33}O$-
h R = Ⓟ-$C_6H_4CH_2OCH_2$-
i R = Ⓟ-$CH_2NH(CH_2)_9$-



8

n-$C_{16}H_{33}$(n-C_4H_9)$_3P^+Br^-$

9



10

10a R = n-$C_{16}H_{33}O$-
b R = Ⓟ-$C_6H_4(CH_2)_6OCH_2$-

tions[11,12] (Table I). In general, the alkylated cryptands are usually better than the regular cryptands and the crowns or phosphonium salts. A detailed examination of the kinetics of reaction (1) under PTC conditions gave the

Table I[a]

Substrate	Reagent	Product	T(°C)	Catalysts: rel. times for reaction completion
n-$C_{18}H_{17}Br$	KI	n-$C_8H_{17}I$	60	1d>D18-C-6[b]>9>7h>7e>7d
n-$C_{18}H_{17}Cl$	KCN	n-$C_8H_{17}CN$	80[c]	7e=9>7d
n-$C_8H_{17}OSO_2Me$	KF	n-$C_8H_{17}F$	120	9>7h
$PhCH_2COMe$	n-BuBr/NaOH	PhCH(n-Bu)COMe	20[d]	9>D18-C-6>7e>7d
n-$C_6H_{13}COMe$	$NaBH_4$[e]	n-$C_6H_{13}CH(OH)Me$	20	9>7e>D18-C-6≅7d

[a]Liquid-liquid PTC in which the substrate was the organic phase, except for the borohydride reductions (benzene solvent); 0.05 mole equilvalent of catalyst, except for 7d (0.01 mol equivalent). [b]D18-C-6 = dicyclohexano-18-crown-6. [c]For 7d, 60°. [d]For D18-C-6, 80°. [e]For 7d, KBH_4.

following rate constants relative to dibenzo-18-crown-6 as 1.00: 7a, 6.15:

$$p\text{-}NO_2C_6H_4CH_2Br + KSCN \longrightarrow p\text{-}NO_2C_6H_4CH_2SCN + KBr \qquad (1)$$

1d, 5.10; dicyclohexano-18-crown-6, 1.65; 18-crown-6, 1.44; decaglyme, 1.41; tetra(n-butyl)ammonium perchlorate, 1.29; benzo-18-crown-6, 1.23; dibenzo-18-crown-16, 1.00; 9, 1.00; Carbowax 20M, 0.83.[13] Despite the obvious excellence of the cryptands, the authors considered them too expensive (no mention of recycling was made) and suggested the preferred use of the more economical onium salts. Both liquid-liquid and solid-liquid[14] PTC's are possible; in the latter case, the reaction mixture can be either homogeneous or hetereogeneous, depending on the quantity of cryptand used. For reaction (2) the homogeneous reaction is about 25 times faster than the liquid-liquid two-phase reaction.[15]

$$n\text{-}C_8H_{17}OSO_2Me + KY + 7e \xrightarrow[\text{or } PhCl/H_2O]{PhCl} n\text{-}C_8H_{17}Y + MeSO_3K \qquad (2)$$

Y = Cl, Br, SCN, N_3, CN

Cryptands such as 7e and 7f can be caused to react with chloromethyl polystyrene to provide an economical polymer-bound catalyst of reasonable activity. Table II shows how these resins compare with both the free cryptand and an analogous crown ether (10). The main problem with such resins is their lack of mechanical strength (resistance to mechanical degradation caused by stirring). Increasing the amount of crosslinking improves the strength of the resin but causes a marked decrease in activity.

Table II

Substrate	Reagent	Product	Catalyst	$t_{1/2}$ (min)	ref.
n-$C_8H_{17}Br$	KI	n-$C_8H_{17}I$	10a	27	16
"	"	"	10b	22	"
"	"	"	7e	250	"
"	"	"	7g	16	"
"	"	"	7h	123	"
"	"	"	7i (1%x.l.)	9	17
"	"	"	7i (2%x.l.)	27	"
"	"	"	7f	3	"

Resins such as 10b and 7i are, however, highly suited for removing lanthanide shift reagents from NMR samples,[18] allowing full recovery of the sample.

Anion Activation/Superbasicity

One reason why the cryptands make such good phase transfer catalysts is that they "activate" the anion, i.e., make it very reactive,[19] either as a nucleophile or as a base. When the cryptand encloses a cation, the effective diameter of that cation is increased considerably (e.g., from 2.7Å to about 10Å for K^+ with C222) and there is a concomitant decrease in the cation-anion interaction. The increased separation of cation from anion, especially in nonpolar aprotic solvents, makes the anion "naked", i.e., virtually unsolvated, and thus very reactive. For those reactions in which participation by the cation is necessary, the addition of a cryptand will slow the reaction. For example, the relative rate of the reduction of acetone by potassium hydrido-(phosphine) ruthenate complexes is halved upon the addition of C222,[20] due to the decrease in polarization of the carbonyl by the cryptated potassium cation. Other carbonyl reactions are similarly affected. When cyclohexanone is treated with butyllithium in diethyl ether, addition at C1 normally occurs. If one adds C221, only enolization occurs.[21] Lithium bromide must be present with C221 to give C1 addition in that case.[22] If excess MeI is present at the outset with cyclohexanone and C221 prior to butyllithium addition, extensive methylation occurs at C2 and C6.[21b] The cyclohexanone enolate exhibits enhanced basicity; when generated without cryptand present, it does not deprotonate either Ph_3CH or Ph_2CH_2, but does so readily with C211 present.[23] This strong non-nucleophilic base dehydrohalogenates cyclohexyl chloride[23] and bromide[21b] to cyclohexene quantitatively within a minute at room temperature.

The basicities of NaH and KH are enhanced in benzene or THF by C221 and C222, respectively. These activated bases can be used to metalate a variety of organic compounds normally difficult to metalate, including ArOH, Ph_3COH, Ph_2NH, $PhNH_2$, $(Me_3Si)_2NH$, Ph_3CH and Ph_2CH_2, all generally in high yields and short reaction times.[24] Potassium hydroxide, activated by C222, can be used to saponify esters normally difficult to saponify, such as methyl mesitoate[25] (Table III).

Table III

Base	Solvent	T(°C)	Time (h)	Yield (%)
KOH(s)	1-propanol	97	5	0
KOH(s)+D18-C-6	1% MeOH in Tol	73.8	31	58
KOH(s)+C222	Tol	25	12	70
KOH+C222 (0.8M)	DMSO	25	0.2	100

Carboxylate anions activated by cryptands in benzene yield esters when caused to react with alkyl halides[26] (Table IV).

Table IV[a]

R^1X	R^2COOK	T(°C)	R^2COOR^1 yield (%)
$PhCH_2Br$	CH_3COOK	15	99
"	CH_3CH_2COOK	15	85
"	$(CH_3)_2CHCOOK$	15	95
n-$C_8H_{17}Br$	CH_3COOK	83	85
"	CH_3CH_2COOK	83	90
"	$(CH_3)_2CHCOOK$	83	99
$BrCH_2CH_2Br$	CH_3CH_2COOK	83	89[b]

[a] From ref. 26b: the catalyst in all cases was C222.
[b] The monobromo ester accounted for the other 11%.

Miscellaneous

The ability of cryptands to solubilize ionic species and to reduce the effects of ion-pairing leads to faster reaction times and/or better yields in a number of reactions, such as the Williamson ether synthesis (Equation (3), Table V).[27] Other reactions, which do not normally occur

$$ROK + R'X + C222 \xrightarrow[RT]{\text{benzene}} ROR' \qquad (3)$$

at all have been effected by the addition of cryptand. Cyclopropyl phenyl

Table V

ROH	R'X	Solvent[a]	Temp (°C)	Time	Yield (%)
cyclooctanol	$PhCH_2Br$	1.2	20	5h	98
cholesterol	"	1.2	20	5h	72
2-butanol	$PhCH{=}CHCH_2Br$	1.2	20	5h	75
"	$n\text{-}C_8H_{17}Br$	1.2	20	5h	32[b]
PhOH	MeI	2	20	6min	100
"	"	2	20	95min	100[c]
"	$(CH_3)_2CHBr$	2	20	6min	95
"	"	2	20	24hr	6[c]
Ph_3COH	MeI	1	20	5min	100
"	"	1	20	60min	10[c]
"	$n\text{-}C_5H_{11}Br$	2	20	5min	20[d]
"	"	2	20	60min	0

[a]Benzene = 1, THF = 2. [b]64% 1-octene formed. [c]Reaction carried out without cryptand. [d]80% alkene formed.

ketone can be methylated via the enol generated by KH and C222[28] in 90% yield; without a cryptand present KH reduces the ketone to the alcohol in 82% yield. A reaction may proceed better in the presence of an increasing amount of cryptand. Such is the case for the alkylation of phthalimide, part of the Gabriel synthesis, and is shown in Table VI.[27b]

Table VI

RX	equiv. C222	Time[a]	Yield (%)[a]
EtBr	1	30sec (2h)	100(100)
"	0.1	1h (12h)	100(100)
$PhCH_2Br$	1	30sec (1h)	98(98)
"	0.1	10min (12h)	98(85)
BuBr	1	10min (1.5h)	90(90)
"	0.1	3h (12h)	85(90)

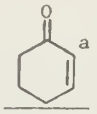
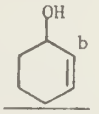
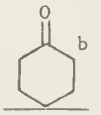
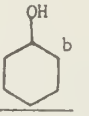
[a]In THF; numbers in parentheses refer to the same reaction in benzene.

The use of a cryptand can also bring about a change in the regio- or stereoselectivity of a reaction. An example of the latter is the Michael addition of methyl chloroacetate to methyl acrylate[29] + NaH in benzene: with no catalyst, substituted cyclopropane product was obtained in 2% total yield, 32% trans; with 18-C-6, 20% total yield, 67% trans;

and with C222, 25% total yield, 80% trans.

As pointed out earlier, cation coordination with a carbonyl oxygen may be required in a reaction. This is true for $LiAlH_4$ reductions, illustrated in Table VII in the results of 2-cyclohexenone reduction.[30] Coordination

Table VII

Solvent/cat.	Time (min)				
Et_2O/none	1 or 15	<2	98	0	2
Et_2O/C211	15	20	23	62	15
THF/none	1 or 15	<2	86	10	4
THF/C211	1	15	14	50	36
THF/C211	15	<2	10	29	61

[a]% recovered. [b]% yield.

of the carbonyl oxygen by the lithium cation favors hydride attack at C1; when the cation is complexed by the cryptand, attack at C3 is preferred. Interestingly, aromatic ketones and aldehydes are not so dependent on this type of cationic assistance,[31] which would allow the selective reduction of these groups in the presence of aliphatic ketones or aldehydes. Such selective reduction has not as yet been investigated.

The replacement of chlorine by fluorine is another reaction that has not been well investigated; only the syntheses of acetyl fluoride from acetyl chloride[32] and tetrachlorofluoropyridine from pentachloropyridine[33] have been examined. Since "naked" fluoride should be a strong nucleophile, further investigation would seem worthwhile.

Since the alkali metals are solubilized by the cryptands in a variety of solvents, including benzene, dissolving metal reductions could be done in such solvents rather than in liquid ammonia. A great potential exists for the two-electron reducing system using $[Na^+ - C222]Na^-$ in $EtNH_2$;[34] as yet, it has not been tried on an organic substrate. Virtually any reaction in which an alkali or alkaline earth salt is used has the possibility of being improved by the use of a cryptand. The use of cryptands can also give insights into reaction mechanisms, as seen in the simple case of the $LiAlH_4$ reduction of cyclohexanone. It is hoped that the information presented here will increase our perception of the tremendous potential of cryptands.

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LC/MS: A PROLEPTIC METHOD IN THE STRUCTURAL DETERMINATION OF BIOLOGICALLY INTERESTING COMPOUNDS

Reported by Tom Holt October 31, 1983

Compounds of interest to biologically oriented chemists are all too frequently highly polar, thermally labile, and generally nonvolatile. Structural studies of such compounds often involve trace quantities in complex matrices such as crude extracts of living matter or hydrolysates of biopolymers. The utility of linking chromatography with mass spectrometry (MS) in these studies has been demonstrated by the now routine use of gas chromatography directly coupled to mass spectrometry (GC/MS).[1] GC/MS analyses, however, require volatile compounds; thus compounds of interest often must be derivatized prior to analysis. With the success and wide application of high performance liquid chromatography (HPLC), especially in solving separation problems of polar biogenic molecules, methods have been sought to link directly liquid chromatography with mass spectrometry (LC/MS).[1,2,3] Since the effective beginning of LC/MS in 1973-74,[4] research has focused primarily on the development of interfacing technology and the application of the technology to model systems. The recent nascence of the application of LC/MS to real problems has demonstrated its viability.

Instrumentation

Ideally, the optimal operation of neither the LC system nor the mass spectrometer should be compromised by the LC/MS interface. In practice, all of the interface designs require some concessions on the part of one or both components. Table I lists a set of ideal parameters necessary to achieve the full analytical potential of the LC separation and MS identification, which illustrates immediately the inherent incompatibilities of the two methods. Obviously the coupling is difficult. The major compromises addressed by the various interfacing techniques can be subsumed under four headings:[3d]

Table I

Table I. Operating Characteristics Desired from an LC/MS Interface[2a]

LC Operation

- No restrictions on solvents
- Gradient elution
- Buffers, volatile and nonvolatile
- Ion-pair reagents
- Flow up to 2.0 mL/min = 200-2000 cm^3/min (gas at STP)

MS Operation

- Maintain vacuum, hence flow < 20 cm^3/min (gas at STP)
- Variety of ionization methods, soft methods desirable
- Low background
- Both (+) and (-) ion mode

Interface Operation

- High enrichment of sample to solvent
- High yield (transfer) of sample reaching MS
- No peak broadening
- Vaporization of low volatility samples (for EI or CI)
- No decomposition of thermally labile samples.

1. Solvent flow: LC solvent flow excessive for MS gas flow.
2. Buffer salts and ion-pair reagents: ionization is per-

turbed; nonvolatile salts cannot be sprayed into ion source.

3. Sensitivity: split LC effluent reduces sensitivity; LC solvents give high background below mass 150.

4. Thermally labile and involatile samples: heating for solvent removal or volatilization of sample for mass analysis may decompose sample.

Of the various types of LC/MS interfaces developed, the most useful fall into two categories; (1) direct introduction, and (2) moving belt. The former can be divided further into the well established direct liquid injection (DLI) interface and the more recent thermospray interface.

Direct Liquid Injection The DLI interface involves the straightforward introduction of the LC effluent into the mass spectrometer. By employing a splitter, only a small fraction of the total effluent is injected into the ion source at a flow rate allowable by the vacuum equipment of the mass spectrometer. Figure 1 represents the DLI interface in its present state of development.[5] Splitting of the effluent occurs at a 2-μm temperature-controlled diaphragm. The fraction passing through the diaphragm enters a heated desolvation chamber and then proceeds, as enriched droplets, into the chemical ionization (CI) source. The remaining solvent functions as the CI reagent gas, or, alternatively, reagent gas is added. With the exception of the original work[4a] and a recent preliminary report,[6] development and applications of the DLI interface have been conducted on quadrupole mass spectrometers.

The solvent flow constraint is the major compromise of the DLI interface. Typically, 1-10% of the LC effluent is diverted to the mass spectrometer. Splitting is not necessary with microbore columns[7] (1 mm i.d. with flow rates of ca. 10-60 μl/min), and as a result, much higher sensitivities are obtained. Since DLI can accept only volatile buffers, the range of LC buffers and ion pair reagents is compromised. The range of MS ionization methods is limited as well; restricted to CIMS, DLI LC/MS cannot be applied to extremely nonvolatile compounds.

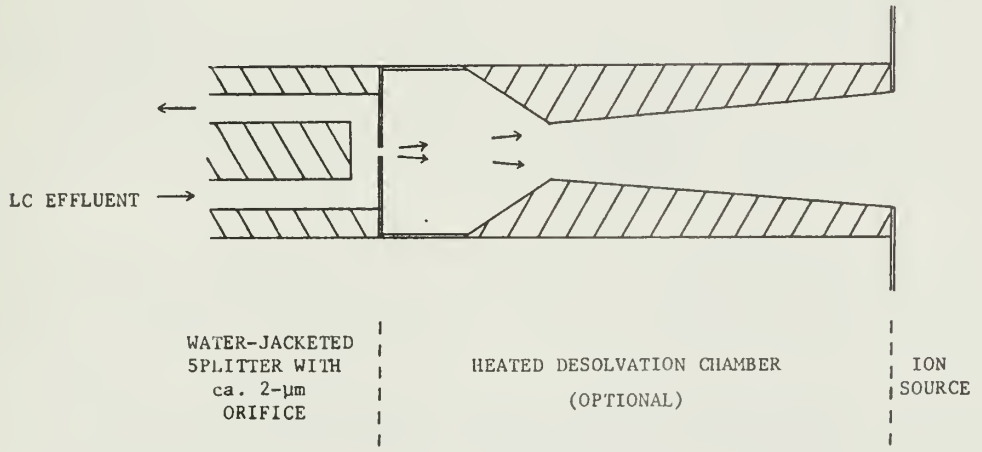


Figure 1. Schematic diagram of the DLI interface.[5]

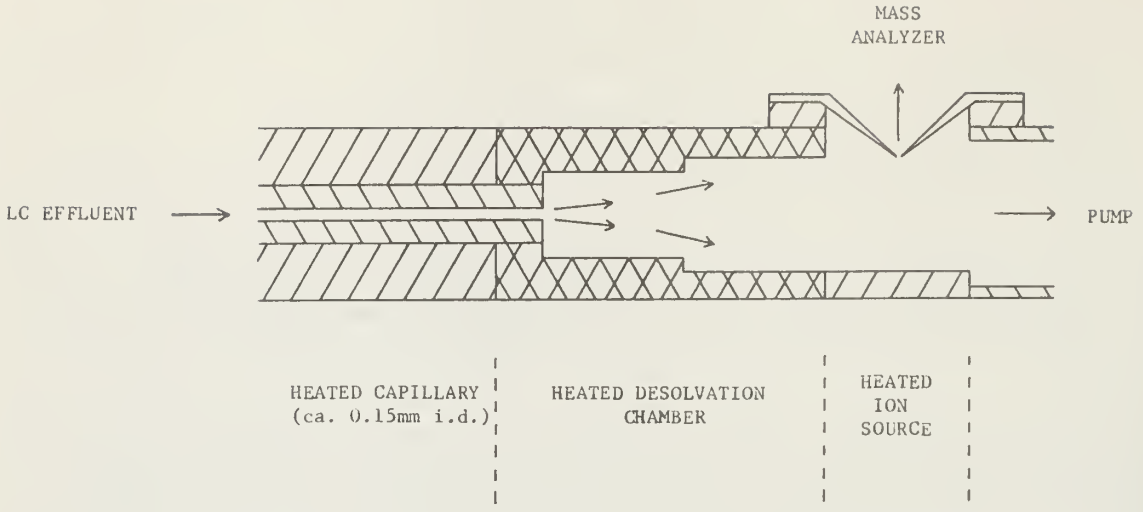


Figure 2. Schematic diagram of the thermospray interface.[9a]

Thermospray. A natural progression in the development of the DLI interface ultimately led to the discovery of a new soft ionization technique. The original approach of Vestal[8] to direct introduction LC/MS employed laser heating at the LC exit to vaporize rapidly both the solvent and the sample. The ensuing effluent jet passed through a skimmer for enrichment before entering either an electron impact (EI) or CI source. Later developments simplified the geometry and the vacuum systems and replaced the laser with an electrically heated vaporizer as shown in Figure 2. It was discovered that, under certain conditions, ions were produced even when the primary ionizing beam was turned off. This new soft ionization technique, termed thermospray,[9] produces mass spectra not unlike those obtained by field desorption (FD) MS. Thermospray LC/MS has been demonstrated with quadrupole instruments only.

Although both involve direct introduction of the LC effluent into the mass spectrometer, the thermospray interface is fundamentally different from the DLI interface. In DLI, the inlet line is cooled to prevent vaporization upstream of the spraying aperture, while in thermospray, controlled partial or complete vaporization of the liquid is accomplished by intense heating of the capillary tube. This produces a supersonic jet of vapor with liquid droplets and solid particles entrained in the jet. As the jet traverses the entrance aperture, up to 50% of the ionized sample, along with 5% of the solvent, enters the analyzer through the aperture. The remaining effluent proceeds directly into the vacuum line.

No external ionizing energy is required in the thermospray ionization process; only thermal energy is supplied. The solvent, however, must contain dissolved, preferably volatile salts. The ionization mechanism appears to be as follows:[10]

1. The majority of solvent is vaporized, producing a supersonic jet. Nonvolatile molecules are preferentially retained in droplets of solvent mist.
2. Since the liquid contains ionic species, droplets of mist are charged positively or negatively according to statistical expectations.

3. Sample molecular ions evaporate or are desorbed from the superheated droplets assisted by the high local electric fields generated by the charge on the drop.

The compromises necessary in thermospray LC/MS are fewer than in DLI LC/MS. The thermospray system is capable of vaporizing up to 2 mL/min of aqueous effluent with up to 50% of the solute entering the mass analyser. For nonvolatile samples, thermospray provides soft ionization that produces a mass spectrum with a strong molecular ion and a low solvent background level; however, less structural information is obtainable compared with CIMS. For thermally labile samples, the heating is severe but over a short time, during which the solute is protected by the surrounding solvent droplet. The solvent must be ionic in thermospray, and, like the DLI interface, buffer selection is compromised by permitting, in practice, only volatile buffers. Limited to quadrupole instruments, the technique cannot achieve the high mass range or high resolution attainable by magnetic instruments.

Moving Belt. As with the direct introduction systems, the moving belt system[11] entails transportation of solvent plus sample, desolvation during transport, and ionization of sample within the source. The sample, together with the solvent, is collected on a belt that moves continuously through several vacuum stages into the source. Figure 3 shows a schematic of the moving belt interface. The belt with the deposited LC effluent is subjected

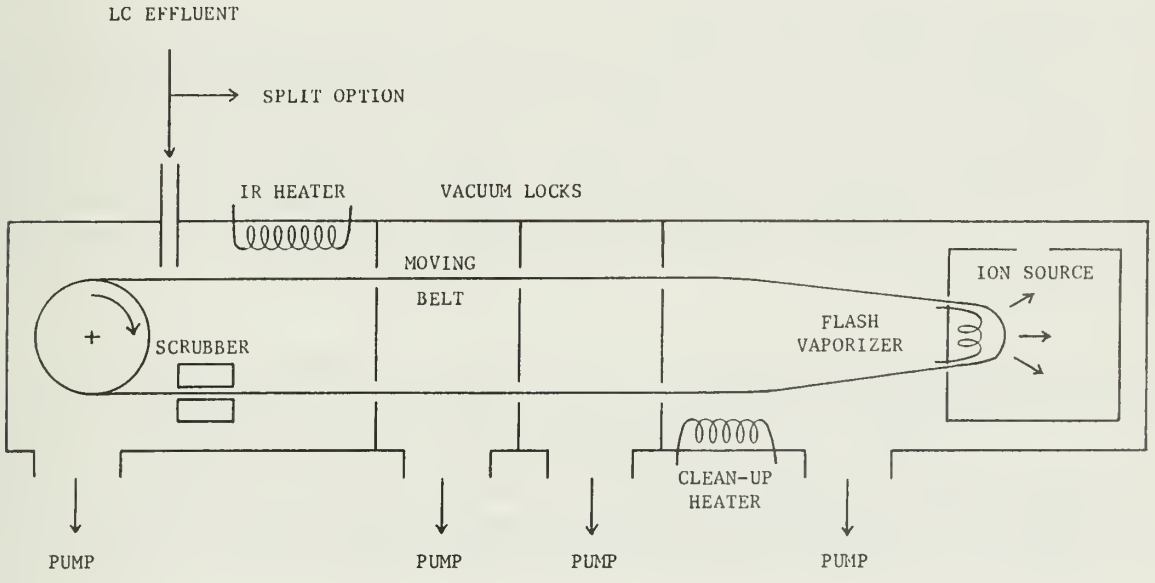


Figure 3. Schematic diagram of the moving belt interface.[2a]

to an IR heater to speed desolvation, or, in more recent work,[12] the LC effluent is nebulized with heated nitrogen and sprayed on the belt, thus obviating the use of a heater. A flash heater in the source volatilizes the sample for either EI- or CIMS, and the interface is compatible with both quadrupole and magnetic sector instruments.

With the moving belt interface, a compromise must be made with solvent flow. The solvent capacity can be as high as 1.0-1.5 mL/min for volatile solvents. However, with aqueous solvents the capacity may fall as low as 0.1 mL/min, thus requiring a splitter. As with the DLI interface, increased sensitivities have been observed with microbore LC columns.[13] The flash evaporator is a potential problem for nonvolatile compounds, and the IR heater, if used, may decompose thermally labile compounds. The interface need not compromise the use of nonvolatile buffers since removal is possible in the scrubber stage. The belt system, like the DLI system, has been limited, in practice, to CIMS. EIMS has also been employed but is not generally useful for the polar compounds often analyzed by LC/MS. More recent work[14,16] has been directed toward the development of fast atom bombardment (FAB) and secondary ion mass spectrometry (SIMS) moving belt systems, perfection of which would greatly expand the scope of compounds amenable to LC/MS analysis.

Applications

Nucleosides. The utility of LC/MS in the separation and identification of nucleosides has been demonstrated by two groups.[17,18] The technique is particularly useful since nucleosides are not amenable to GC/MS without prior derivatization. One study[17] examined model mixtures of underivatized purine and pyrimidine nucleosides using DLI LC/MS. In a mixture of hypoxanthine, xanthine, adenine, adenosine, uridine, uracil and thymidine, four of the components were readily separated and identified (25-30 μg/compound injected). Of the other three, uracil (M_r= 112) was lost in the mass spectral background, and selective ion monitoring was required for identification of xanthine and hypoxanthine, which were not resolved by LC.

Another model study applied LC/MS to the search for minor, post-transcriptionally modified nucleosides in transfer RNA hydrolysate mixtures.[18] In studies of this type, the compounds of interest are typically 1-2% of the mixture and the total sample is limited (1-100 μg). LC/MS had clear advantages over conventional LC, which relies solely on retention time for identification, and over GC/MS, which requires preparation of volatile derivatives. Using thermospray LC/MS, nine minor nucleosides were identified in a 10-μg sample of rabbit liver $tRNA^{Val}$ hydrolysate. Identifications were based mainly on protonated molecular ions and protonated nucleoside base ions.

Peptide sequencing. The analysis of derivatized partial and total hydrolysates of peptides by GC/MS has become a routine method in peptide sequencing.[19] The length of the oligopeptide amenable to this method is limited by the volatility of its derivative, the upper limit being four to six amino acid residues. This constraint, in turn, limits the length of peptide applicable to GC/MS sequencing; for polypeptides of 50 or more residues, fragments longer than hexapeptides are generally needed for unambiguous sequencing.

In theory, LC/MS can provide an ideal solution to the problems inherent in GC/MS sequencing. LC is not limited by the volatility of the oligopeptide; accordingly, no derivatization is required. Furthermore, MS (using FAB ionization) has shown great utility in giving sequence information for underivatized peptides as large as hexadecapeptides.[20] In practice, LC/MS has exhibited the same constraints as GC/MS. The major compromise in the method is the ionization step. CIMS is limited to underivatized peptides of six or fewer amino acid residues.[21] In order to

make the technique useful for peptides larger than hexapeptides, the application of LC/MS to peptide sequencing has entailed derivatization of peptide mixtures prior to LC and CIMS analysis.[22,23,24] No examples of sequencing underivatized peptides by LC/MS have appeared in the literature.

A DLI interface was used in an early model study of LC/MS.[22] Model mixtures of up to six N-acetylpeptide methyl esters (2.5 nmol/peptide injected) containing three to eight amino acids were analyzed. Using CIMS, it was possible to obtain complete sequence information for all components in many, but not all, of the mixtures. Interpretation of the results was complicated by the presence of numerous side-products formed in the derivatization process. The authors concluded that the derivatization step was the Achilles' heel in the method and that possible solutions were: (1) optimization of the derivatization procedure, or (2) utilization of an ionization technique applicable to underivatized peptides.

Sequencing employing the moving belt interface with CI/EI has been carried out on model mixtures of up to eight di- to tetrapeptides.[23] The N-acetyl-N,O,S-permethylated derivatives were separated by reversed phase LC (ca. 5 nmol/peptide injected), but over- and undermethylated products hindered clean separation. The moving belt interface equipped with both a heated nitrogen-spray deposition and an IR heater allowed up to a 50% split of the 1 mL/min acetonitrile-water (30:70) effluent. The CI mode was generally more useful than EI, and all sequence peaks were exhibited. In a similar study,[24] only partially interpretable results were obtainable with real mixtures of protein origin. The high-level impurity background, likely from the derivatization, obscured the LC resolution. These studies, as with the DLI sequencing, illustrate the need for a non-derivatization approach to LC/MS sequencing.

Crude extracts. Chloroform extracts of the tropical plants Imperatoria ostruthium and Calophyllum inophyllum are rich sources of coumarins. In a search for novel coumarins by GC/MS, it was discovered that coumarins in some extracts decomposed in the GC column.[25] Analysis of other extracts employed LC/MS with the moving belt interface to avoid this problem.[13] Using microbore LC, 14 coumarins were separated from plant extracts and ten were identified by their CI mass spectra and retention times.

In another application of LC/MS to natural products, chloroform extracts of ergot fermentation broths were analyzed by LC/MS to identify the ergot alkaloids present, with the future goal of elucidating the biosynthetic pathways of these alkaloids.[26] By utilizing LC/MS, the larger and more polar alkaloids not amenable to GC/MS could be analyzed. When an EI/CI moving belt interface was used, 11 alkaloids were identified in a real mixture of 18 unknowns. Identification was based on the EI and CI mass spectra.

LC/MS has also been applied to the study of epidioxy sterols from marine sources.[27] Previous studies by GC/MS[28] required reduction and trimethylsilylation of the sterol peroxides to the corresponding trimethylsilyl ethers prior to analysis. In order to assess the application of LC/MS to this problem, with the obvious benefit of no prior derivatization, purified extracts of the sea hare, Aplysia dactylomela, and the tunicate, Ascidia nigra, were analyzed by DLI LC/MS. With the use of ca. 10-μg injections, two epidioxy sterols were found in the A. dactylomela extract and four in the A. nigra extract. Identification was based on comparison of mass spectral fragmentations with known standards.

Glucuronides. Glucuronides are polar, nonvolatile, thermally labile compounds which are of special biological interest since glucuronidation is a major mammalian conjugation pathway,[29] and intracellular glucuronidase activity has implications in the design of anti-cancer drugs.[30] Without modification, the glucuronides are intractable by GC or EIMS and can be analyzed only with difficulty by CIMS.[31] By contrast, thermospray LC/MS has been applied successfully to glucuronide mixtures.[32] A model mixture of three glucuronides was separated by reversed phase LC, and the components were identified by positive and negative ion MS (ca. 0.1 nmol/compound injected). In the same study, diasteriomeric glucuronides of propranolol, formed by in vitro incubation of racemic propranolol with immobilized rabbit glucuronyltransferase, were separated and identified by LC/MS.

Prospects

In summary, LC/MS is limited by the ionization method. CI, the current ionization method for both DLI and moving belt LC/MS, requires prior volatilization of the sample for ionization in the gaseous state. Compounds that cannot be volatilized intact in the ion source are intractable. The most exciting prospect for LC/MS is the application of solution and solid state ionization techniques such as thermospray, FAB, and SIMS, which do not require prior volatilization. Thermospray MS has demostrated a capability to ionize large, highly-polar nonvolatile compounds such as glucagon, a 29-amino acid polypeptide (M_r= 3550).[33] Unfortunately, the technique is limited by the inherent low mass range of quadrupole instruments; indeed, glucagon was seen only as the doubly- and triply-charged protonated molecular ions. Additionally, thermospray fails to provide useful structural information on large molecules, such as sequence information on peptides.[33] Some preliminary results have been reported for moving belt systems employing FAB[14] and SIMS[16] ionization, arguably the most useful ionization method for polar, high molecular weight compounds.[20] Although the method has yet to be perfected, its success could make the belt system with FAB or SIMS the method of choice for nonvolatile polar compounds.

In the application to problems of biological interest, the LC/MS technique is still proleptic. It is here, in the sense that its potentiality has been demonstrated in some model and simple real systems; but it is not here yet, in the sense that LC/MS is still undergoing rapid development and has yet to be essential in the solution of major structural problems. The new soft ionization techniques, systems employing thermospray, FAB, or SIMS, may well bring LC/MS into routine use in the near future.

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ISOTOPIC PERTURBATION OF ^{13}C NMR SPECTRA FOR DISTINGUISHING BETWEEN SYMMETRICAL AND RAPIDLY EQUILIBRATING MOLECULES

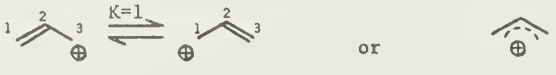
Reported by Douglas R. Chrisope November 3, 1983

In a number of interesting cases, chemists face the problem of whether a compound is an equilibrium mixture of rapidly rearranging species or has a static, symmetrical structure. In thermodynamic terms, the question is whether there is a single energy minimum or whether there are several minima separated by small barriers. This issue bears directly on our understanding of structure, bonding, and reaction mechanisms and can affect synthetic methodology. The recently developed technique of isotopic perturbation of ^{13}C NMR spectra has proven to be a uniquely powerful tool for resolving a number of previously ambiguous cases of this type.[1] The technique can be understood with a basic knowledge of dynamic NMR (DNMR) and deuterium isotope effects on ^{13}C NMR chemical shifts.

Dynamic NMR is the currently favored method for direct observation of equilibrium processes.[2] Peaks that are averaged by fast rearrangements may be separated by cooling the sample. If the slow exchange spectrum (in which no changes occur on further cooling) is available, then a complete lineshape analysis can provide a very accurate determination of the barrier height for the process. The problem is that slow exchange spectra are often not available since slowing rearrangements with barrier heights below ca. 5 kcal/mol requires temperatures not accessible with commercial variable temperature units. Molecules undergoing such rearrangements cannot be distinguished from static, symmetrical species by DNMR alone. The isotopic perturbation method is independent of the barrier height, and no attempts to slow down a rearrangement are required.

The effects of deuterium substitution on ^{13}C NMR shifts must also be recognized. Nearly any type of ^{13}C resonance will be shifted upfield by 0.2 - 0.4 ppm upon replacement of an attached proton by deuterium, and this effect is additive.[3] The upfield shift was explained by Gutowsky[4] as resulting from zero point energy differences. Since the vibrational amplitude of a C-D bond is smaller than that of a C-H bond, the bonding electrons are, on average, closer to the carbon in the deuterio compound. Consequently, the carbon nucleus experiences greater shielding than in the protio analog. Carbons further away also exhibit this effect, although the effect is attenuated.[3]

The isotopic perturbation method can be illustrated by a simple, hypothetical example. Allyl cation could conceivably have two limiting structural possibilities, a pair of equilibrating allylic cations, A, or a static, symmetrical species, B. Situation A represents a degenerate equilibrium

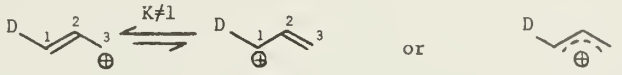


A B

with, presumably, a low barrier. Carbons 1 and 3 would each have the same average environment, giving a single NMR peak halfway between the vinyl region (estimated as δ 120 ppm) and the cation region (estimated as 330 ppm) or at about 225 ppm. Structure B, with identical terminal carbons that

are sp^2 hybridized and deshielded by the positive charge might also be expected to have a peak around 225 ppm.

Now, consider the possibilities with a single deuterium atom on one terminal carbon. The magnitude of an energy alteration upon deuterium



A B

substitution depends on the bond type to the heavy atom. In case A, the deuterium experiences different bond types and charge environments in the separate species, and their energies are no longer equal. Empirical data suggest that the equilibrium will shift to the left. Carbon 1 is thus a vinyl carbon in a majority of the molecules, and its NMR signal would shift upfield toward the vinyl region to reflect the new equilibrium. Carbon 3 has increased positive charge and its NMR signal would be expected to shift downfield. For a typical change in the equilibrium constant of ca. 15%, these shifts would be 25-50 ppm (vide infra). The characteristic features of a deuterium-substituted equilibrating system are shown in Figure 1. Carbon 1 may also be broadened or split by spin-spin coupling to deuterium, with a maximum coupling constant of ca. 25 Hz.[3] In case B, the only change from the unlabeled spectrum is the intrinsic isotope effect of deuterium, and carbon 1 would shift ca. 0.2 - 0.4 ppm upfield and appear as a triplet.

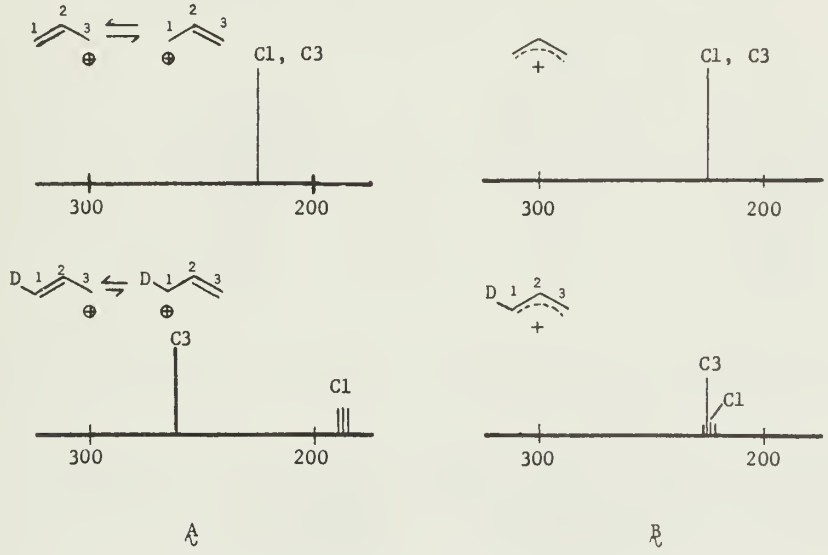


Figure 1. Effects of deuteration on ^{13}C NMR spectra.

Carbon 3 is still a singlet in the original position (Figure 1). Also, the deuterated carbon may suffer a loss of NOE and less efficient dipolar relaxation, both of which would decrease the peak intensity. The results expected for these two cases would be clearly different.

The spectral appearance for a particular case can be predicted by standard DNMR equations.[2] For equilibrating species, Δ is the frequency difference of the peaks being averaged. On isotopic perturbation, the averaged line splits, appearing at new frequencies $f_1 = \frac{\Delta}{K+1}$ and $f_2 = -\frac{K\Delta}{K+1}$.

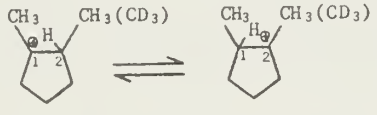
The separation between these lines is defined as $\delta_{pert} = f_2 - f_1 = \frac{\Delta(K-1)}{K+1}$. Since Δ is determined from the slow exchange spectrum, it may not be available directly, and model compounds are important. K can be increased by incorporating more deuterium and/or lowering the temperature.

The method is therefore an isotope perturbation of a degenerate equilibrium as detected by ^{13}C NMR. It is assumed that any degenerate equilibrium will be shifted on D substitution. Peak splitting in equilibrium cases must have the expected temperature dependence and can be characterized regardless of rate. The presence of a single species is demonstrated by the expected small isotope effect on chemical shift.

Equilibrium cases

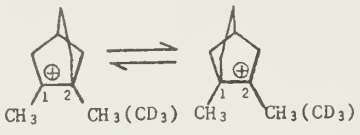
Saunders' first report in 1977 focused on equilibrating cations.[5] The cyclopentane derivatives 1 and 2 cannot be frozen out with normal techniques, indicating either a symmetrical structure or a maximum rearrangement barrier of 3-4 kcal/mol. The ^{13}C NMR data for 1-d_3 and 2-d_3 listed in Table I clearly show the temperature dependence of the large splitting of C1 and C2. This confirms the presence of equilibria in both 1 and 2.

Table I



1

T, °C	δ_{pert} (ppm)
-142	81.8
-126	73.0
-110	65.0
-95	59.4
-81	55.7
-45	45.4

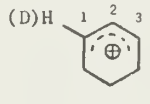


2

T, °C	δ_{pert} (ppm)
-127	20.5
-119	19.1
-89	16.4
-60	13.8
-40	12.6
-21	11.9

Symmetrical cases

As an illustration of a system involving a single species, Saunders investigated cyclohexenyl cations. The unlabeled compound 3 exhibits a single peak near 223 ppm for carbons 1 and 3. Monodeuteration at C1 moves



3

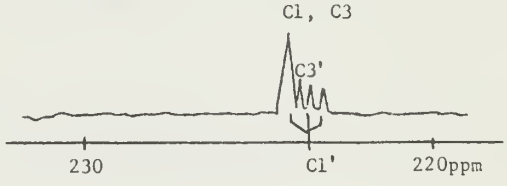


Figure 2. 67.9 MHz ^{13}C NMR spectrum of 1:4 mixture of 3 and 3-d.

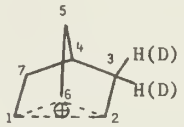
the C3 line 11.4 Hz upfield and C1 is a 1:1:1 triplet 17 Hz beyond that, as shown in Figure 2. No other changes occur in the spectrum. These

small shifts are consistent only with intrinsic isotope effects on a single, symmetrical structure.

Saunders reported in 1980 the application of his technique to the controversial 2-norbornyl cation.[7] Since 1962, H. C. Brown has insisted that the structure is a rapidly equilibrating pair of classical ions 4a and 4b.[8]



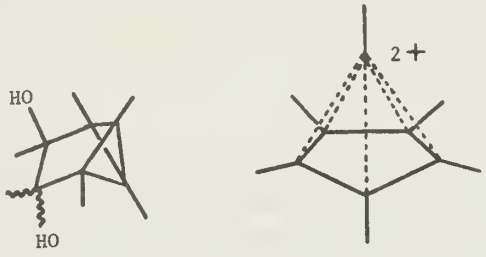
4a 4b



5

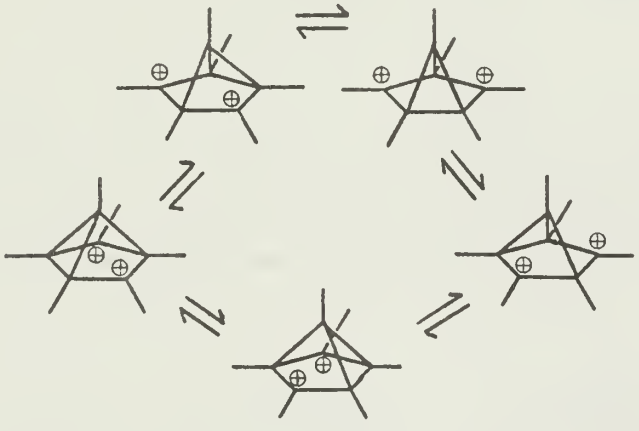
Evidence gathered by Olah and others supports the σ-bridged or non-classical ion structure 5.[9] Saunders' experiment was complicated by 6,2- and 3,2-hydride shifts, but suitable controls and monitoring by ^{1}H and ^{2}H NMR revealed no scrambling of the deuterium in 5-d_2 during ^{13}C NMR data acquisition. The carbon spectrum at -150°C shows a broad (2.3 ppm) peak at 125 ppm, assigned to carbons 1 and 2. Any shift due to perturbation is therefore less than 2.3 ppm, a value consistent only with the non-classical structure.

Hogeveen used the technique to study an interesting dication.[10] Solution of diol 6 in superacid produces a dication with an NMR spectrum consistent with either of two structures, 7 or 8. The unusually high-field



6 7

peak of the apical methyl carbon (-3 ppm) and low temperature ^{1}H NMR data argue for the symmetrical structure. Replacement of one or two of the basal



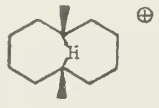
8

methyl groups with CD_3 caused the adjacent ring carbon peak to be split by ca. 0.5 ppm. In the 90.52 MHz ^{13}C spectrum, this separation did not change from -60° to -10°C. The small, temperature-independent splitting was considered conclusive evidence for the novel pyramidal structure with extensive σ-bridging.

Another unusual structure was established by Sorensen and co-workers.[11] Ionization of 1,6-dimethylcyclodecanol in superacid gave a species for which the ^1H NMR spectrum featured a signal at δ-3.9. The ^{13}C NMR spectrum revealed that this proton was coupled to two low-field carbons with $^1J_{CH}$ = 35 Hz. The two structures considered consistent with these data were 9 and 10. The ^{13}C NMR peak at 142.0 ppm was assigned to the methyl-bearing ring



9



10

carbons. Upon introduction of a CD_3 group, this peak was split by ca. 0.6 ppm, independent of temperature. The result was taken as convincing evidence for the symmetrical μ-hydrido bridged cation 10.

The isotopic perturbation method has been applied to several other cations including the cyclobutyl-cyclopropylcarbinyl system,[12] the 9-barbaralyl cation,[13] the Coates cation,[14] and several bicyclo[2.1.1]hexyl cations.[15]

Neutral Molecules

Neutral molecules have also been studied by isotopic perturbation, but with less dramatic results. The chemical shift differences of any carbons that may be averaged by rearrangements are often much less than in the cationic cases. For example, the cyclobutadiene derivative 11 studied by Maier[16] has vinyl carbons 1 and 3 averaged by a rapid equilibrium that could



11

not be frozen out at -185°C. A perdeuterated t-butyl group at C1 caused only a small, temperature-dependent splitting (0.3 ppm at -62°C to 0.45 ppm at -96°C), as expected for an equilibrium process.

The valence isomerization of 1,5-dimethyl-semibullvalene (12) was investigated by Askani.[17] A temperature-dependent splitting of ca. 0.2 ppm



12

was observed upon introduction of a single deuterium atom, which preferred the cyclopropyl position. The equilibrium constant K was estimated as 1.11 (toward this preference) at 29°C and 1.19 at -53°C.

Another neutral species is of interest because isotopic perturbation of its EPR spectrum has been observed.[18] Monodeuteration of the cyclopentadienyl radical reveals that an equilibrium of positional isomers exists in this system.

Organometallic Species

Organometallics provide a very promising area for applications of Saunders' technique. Cyclopentadienyl complexes of transition metals may have either a symmetrical, pentahapto structure or an unsymmetrical, monohapto structure in which the metal migrates rapidly around the ring. Distinction between the two is often difficult by NMR spectroscopy. A 1:1 mixture of $(\eta^5\text{-}C_5H_4D)_2Fe$ and $(\eta^5\text{-}C_5H_5)_2Fe$ gives the proton-coupled ^{13}C NMR spectrum in Figure 3.[19] The large doublet is assigned to ring carbons bearing protons. The deuterated carbon appears as a 1:1:1 triplet upfield

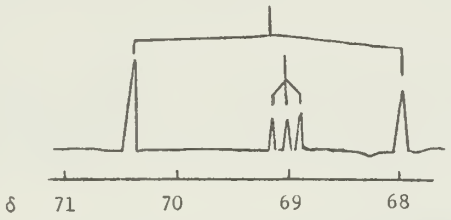


Figure 3. 67.9 MHz ^{13}C NMR spectrum of $(\eta^5\text{-}C_5H_4D)_2Fe$ and $(\eta^5C_5H_5)_2Fe$.

from the doublet's center and the separation is temperature independent, in agreement with the static structure. A 4:1 mixture of $(\eta^1\text{-}C_5H_4D)Sn(CH_3)_3$ and $(\eta^1\text{-}C_5H_5)Sn(CH_3)_3$ (a known fluxional, monohapto system) gave the spectrum in Figure 4. The triplet for the labeled carbon is now downfield

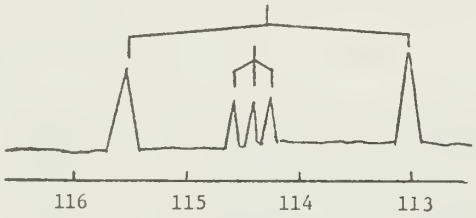


Figure 4. 67.9 MHz ^{13}C NMR spectrum of 4:1 mixture of $(\eta^1\text{-}C_5H_4D)Sn(CH_3)_3$ and $(\eta^1\text{-}C_5H_5)Sn(CH_3)_3$.

of the other ring carbons and the separation is temperature dependent, indicating an equilibrium. Since the magnitude of δ_{pert} is very close to that of the intrinsic isotope effect, unknowns similar to these must be examined with great caution.

In 1980, Schlosser,[20] Schleyer[21] and Bywater[22] independently reported the application of the isotopic perturbation method to various metal-allyl compounds. For allyllithium, the symmetrical trihapto structure and an equilibrium of σ-bonded structures cannot be distinguished by NMR, even at -155°C. Scheyler's 25.2 MHz, proton-coupled spectrum, taken at -60°C, of monodeuterated allyllithium is shown in Figure 5. The barely detectable splitting

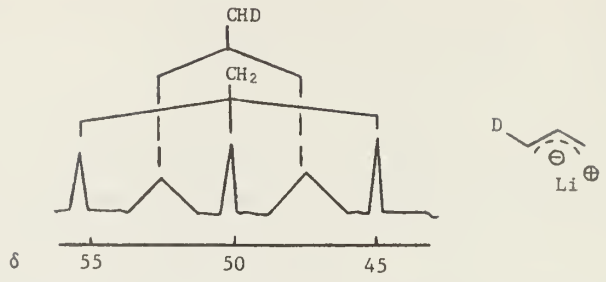


Figure 5. 25.2 MHz, proton-coupled ^{13}C NMR spectrum of allyllithium -d, at -60°C.

was taken as evidence for the symmetrical π-bonded compound. Schlosser's experiment was at 25°C where sharper peaks should improve the chemical shift determinations. The deuterium-bearing carbon was found 0.1 ppm downfield from the unlabeled carbon. This is in the opposite direction expected for an isotope effect on a chemical shift, and Schlosser concluded the structure was π-bonded but slightly asymmetrical and fluxional.[20a] A later full report from the same laboratory[20b] gave the value as 0.19 ppm upfield, as expected for a symmetrical structure, but the original conclusion was maintained. Schleyer criticized this work for overinterpreting the data.[23] An analogous experiment showed allylpotassium to be a symmetrical molecule by virtue of a 0.2 ppm upfield shift for the deuterated carbon.[20a] Allylmagnesium bromide, on the other hand, proved to be an equilibrium mixture. The deuterated carbon moved upfield 0.5 ppm and the other terminal carbon moved downfield 0.9 ppm relative to the unlabeled material.

Other applications of the technique to organometallic systems involve various transition metal complexes with dienes or with bridging methyl ligands.[24-28] Titanocyclobutanes has also been examined.[29]

Variations

Variations on the technique described here rely upon molecules enriched with other heavy isotopes, such as ^{13}C and ^{17}O,[30,31] to perturb the system.

Conclusion

Isotopic perturbation should be considered, where it can be applied, as the method of choice for distinguishing between symmetrical molecules and those involving dynamic equilibria of less symmetrical species. Under the assumption that the appropriately labeled compounds can be made available and ^{13}C NMR assignments are unambiguous, the major requirement is insuring that the magnitude and/or direction of the splittings are clearly different for the possible structures. This requirement is usually not difficult to meet, especially with the aid of model compounds. Saunder's powerful technique makes possible straightforward distinctions that were previously inferred and ambiguous.

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SOME SELECTIVE REACTIONS WITH ORGANOALUMINUMS

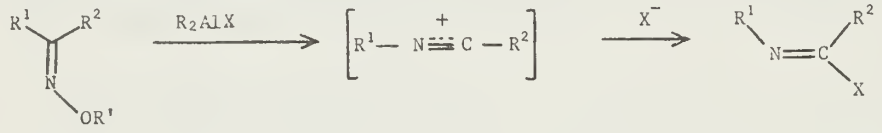
Reported by Athanasios Tsipouras November 7, 1983

Organoaluminums have been in the fore of the olefin-oriented world of petrochemicals for more than thirty years, following two important discoveries by Ziegler and his coworkers.[1a]

The first of these discoveries was the direct synthesis of trialkylaluminums from aluminum metal, olefins and hydrogen. The second was the formation of carbon-carbon bonds by the addition of alkylaluminum compounds to olefins, a reaction of obvious importance to polymer chemistry.

In organic synthesis, by contrast, only recently have organoaluminums begun to be appreciated as general and versatile reagents.[1] The two most important properties of organoaluminums, for the synthetic organic chemist, are a) their ability to act as Lewis acids and b) their ability to act as anion sources. A number of synthetic methods have been developed that take advantage of either or both the above properties. In this seminar, we will concentrate on three such methods: a) the organoaluminum-promoted Beckmann rearrangement of oxime sulfonates,[2] b) isomerization of oxiranes into allyl alcohols by means of organoaluminum reagents[3] and c) the use of aluminum enolates in aldol condensation reactions.[4]

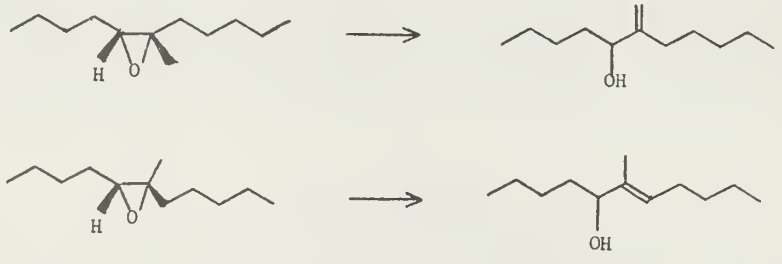
Thus, upon treatment of oxime sulfonates with organoaluminum reagents, Beckmann rearrangement occurs with simultaneous nucleophilic trapping of the intermediary iminocarbocation (1).



(1)

This reaction provides a highly efficient route to imino thioethers, imino nitriles and α-alkylated amines, as examples. Moreover, α,α-dialkylation of amines can be accomplished by the successive treatment of oxime sulfonates with trialkylaluminum followed by Grignard reagents.

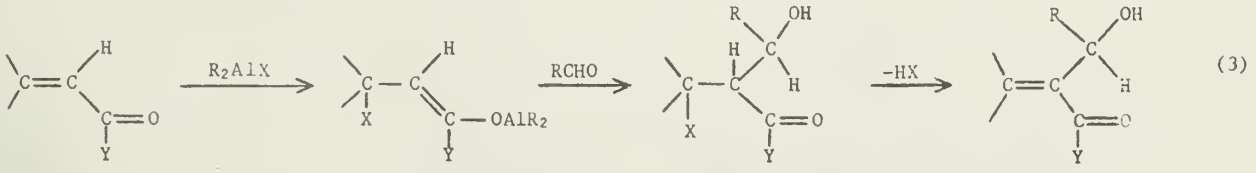
Oxiranes can be isomerized into allyl alcohols both stereo- and regioselectively by means of an organoaluminum reagent, diethylaluminum 2,2,6,6-tetramethylpiperidide (2).



(2)

The reaction proceeds under mild conditions, in high yields, and complements nicely the existing methods for achieving the above transformation. The further regiospecific transformation of allyl alcohols into 1,3-dienes is also possible.

Aluminum enolates are finding increasing application in aldol condensation reactions, in part due to their availability by methods not applicable for the preparation of other enolates. For example, reagents of type R_2AlX readily add 1,4 to α,β-unsaturated carbonyl compounds. The resulting aluminum enolates react with aldehydes to give aldol adducts in fair to good yields (3).[4a]



(3)

Organoaluminums have recently been used to extend the scope of reactions, traditionally catalyzed by Lewis acids such as $AlCl_3$ and $ZnCl_2$.[5] With alkylaluminum halides, Lewis acid-catalyzed reactions can be run under aprotic conditions, even when acidic protons are produced in the reaction, because alkylaluminum halides react with Brønsted acids to liberate an alkane and generate a new Lewis acid. Thus, ene, Diels-Alder, Claisen and other reactions have been catalyzed using these reagents.

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STEREOCHEMICAL CONTROL OF DIENE CYCLOADDITIONS IN THE SOLID STATE

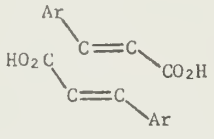
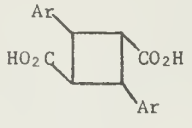
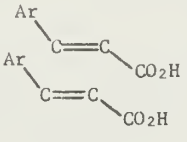
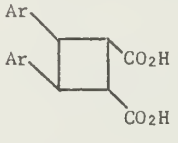
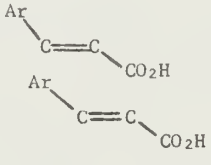
Reported by John Matthews November 10, 1983

Crystals can be classified by symmetry into 230 unique space groups. Space groups which have no symmetry element that changes the chirality of a molecule (i.e., mirror plane, glide plane, inversion center) are known as chiral space groups. In order for a crystal to accomodate only one of a pair of enantiomers, it must belong to a chiral space group. Also, a compound that crystallizes in such a space group can exist in two enantiomeric crystal modifications even if the molecule is achiral.

Solid state reactions in a chiral crystalline environment may provide a method of asymmetric induction.[1] This report will describe the use of such an approach to control the stereochemistry of the photochemical [2+2] cycloaddition of a series of dienes.

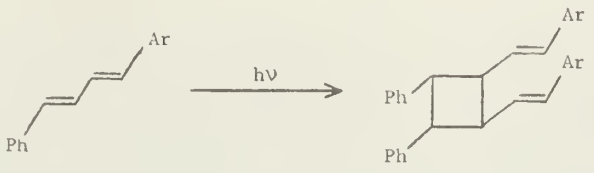
The effect of crystal structure on the products of photodimerizations was first established by Schmidt and coworkers[2] with a series of cinnamic acids. The trans acids often crystallize in more than one polymorphic form. Each modification can be placed in one of three categories (Table I). The

Table I

modification	packing type	irradiation product
α		 truxillic acid
β		 truxinic acid
γ		no reaction

results showed that a distance of 4.0 ± 0.3Å between adjacent double bonds is necessary for dimerization to occur. Crystals of the α and β forms have the necessary spacing, but give different products due to the different packing. In the γ form, distances between all double bonds are 4.7Å or greater, and dimerization does not occur. The trans configuration was retained in each case. The same principles can be applied to dimerizations of cinnamides,[3] quinones,[4] heterocycles,[5] and butadienes.[6] In addition to the distance between adjacent double bonds, the importance of a favorable orientation of the participating orbitals has been shown in some cases.[7,8]

The 4Å rule cannot fully explain the solid state photochemistry of 1. Although both double bonds have the necessary 4Å spacing, only one is reac-

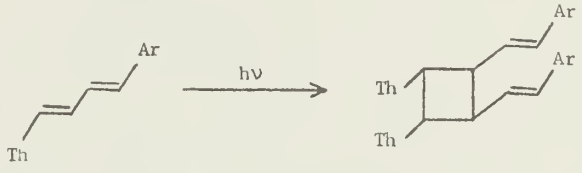


1 2

Ar = 2,6-dichlorophenyl

tive.[6b] The 2,6-dichlorophenyl group is twisted out of the plane of the double bond by 40°.[9] The resulting steric hindrance may prevent dimerization at that location.

Dimerization of the thienyl diene 3 is analogous to that of 1. Because 1 and 3 each crystallize in a chiral space group, a solid solution of the two

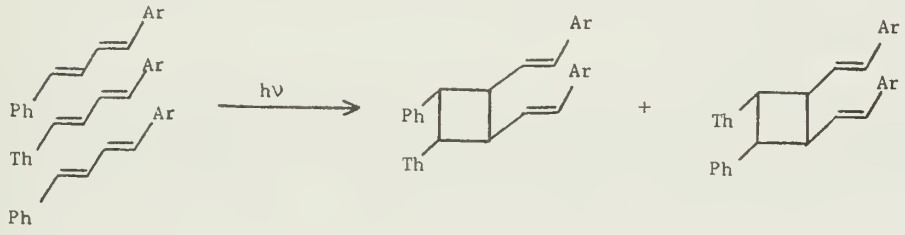


3 4

Th = 2-thienyl

dienes may be expected to give a chiral heterodimer (Scheme I).

Scheme I.

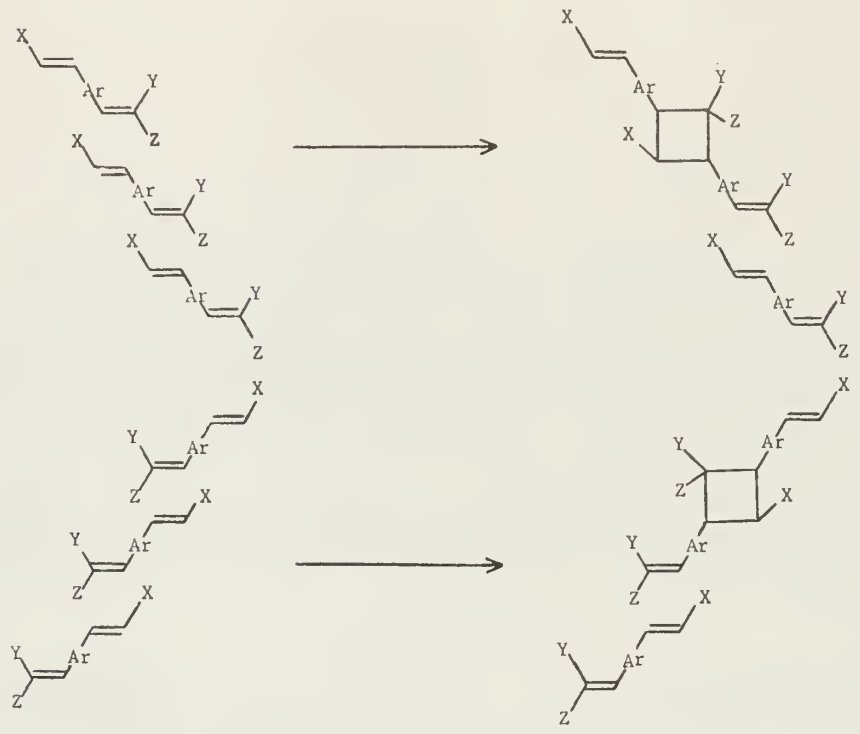


Mixed crystals of 1 and 3 were irradiated under conditions chosen to minimize the formation of homodimers 2 and 4.[10] Diene 3 absorbs at slightly longer wavelength (λmax = 335nm) than does 1 (λmax = 317nm). Irradiation was carried out at >400nm in order to excite 3 selectively, thus minimizing the formation of dimer 2. The yield of 4 can be minimized by using an excess of 1, which will reduce the number of contacts between adjacent molecules of 3. Mixed crystals with a 17:3 ratio of 1 to 3 were prepared from the melt; the dimer mixture obtained by irradiation was composed of 90% heterodimer.

Although irradiation of a polycrystalline sample of a solid solution of 1 and 3 gave a racemic mixture of the two enantiomeric heterodimers, optically active products were obtained from single crystals. Excesses of both configurations were obtained; the optical yield was estimated to be 70%.[1] While the packing of the ground state molecule does not predict an excess of one enantiomer, the excited state from 3 may achieve a preference for one direction of attack due to the influence of asymmetric crystal forces. Theoretical work was done on the system[11] using an extension of the consistent force field method (QCFF/PI)[12] and assuming the involvement of an excimer intermediate. The results supported a preferential direction of attack.

Another approach to an asymmetric cycloaddition involves reaction between two chemically non-equivalent double bonds (Scheme II). A series

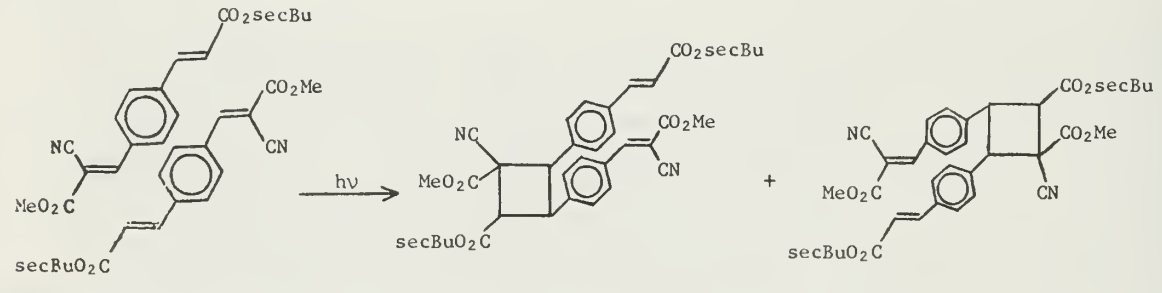
Scheme II.



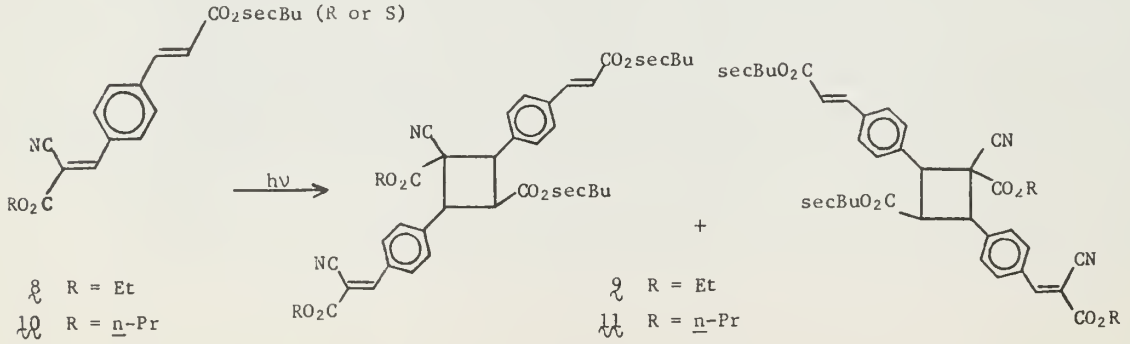
of p-phenylene diacrylates has the packing arrangement shown in Scheme II and the desired 4Å spacing between double bonds. Polymerization in several of these compounds was shown to be controlled by the monomer lattice.[13] Such compounds, when crystallizing in chiral space groups, show potential for an asymmetric dimerization.

The use of chiral monomers, such as dienes 5 and 8 studied by Lahav and coworkers, increases the chance of crystallization in a chiral space group.[14] The packing of 5, shown in Scheme III, leads to equal amounts of

Scheme III.



5 6 7



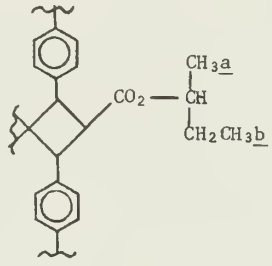
8 R = Et
10 R = n-Pr

9 R = Et
11 R = n-Pr

diastereomers 6 and 7 instead of the desired 1,3-diaryl dimer. Monomer 8, however, was found to crystallize in the motif shown in Scheme II.[15]

Powder samples of 8 were irradiated through pyrex (>300nm) at 5°C; an alternate procedure involved irradiation of monomer suspended in aqueous methanol at -2°C. Dimer 9 was obtained along with trimers and oligomers. In general, dimers in larger relative yields were obtained from the first procedure. Optically pure samples of S-(+)-8, chiral due to the secondary butyl group, gave cyclobutane rings of absolute configuration SSSS upon irradiation. Dimers, trimers, and oligomers had the same absolute configuration. The diastereomeric excess was quantitative within experimental error. The sensitivity of the ^{1}H NMR spectrum to the relative configuration of the cyclobutane ring (Table II) was used to determine the excess. Irradiation of R-(-)-8 gave products of RRRR configuration.

Table II



absolute configuration of cyclobutane ring	absolute configuration of sec-butyl group	methyl a $\delta(CDCl_3)$	methyl b $\delta(CDCl_3)$
SSSS	S	0.52	0.80
RRRR	R	0.52	0.80
SSSS	R	1.10	0.38
RRRR	S	1.10	0.38

Irradiation of less optically pure samples of 8 can give an indication of whether the stereochemistry of the reaction is controlled by the chirality of the crystal or that of the secondary butyl group. Crystals were prepared by melting mixtures of R and S 8 in the desired compositions followed by slow cooling (1°C/2-3 days). Studies were done to determine if R and S molecules were randomly distributed in the crystal or if there were some order.[16] Mixed crystals of deuterium-labeled R and unlabeled S monomers were irradiated. Mass spectrometry of the product showed a statistical distribution of RR, SS, and RS dimers, indicating a random distribution of R and S esters.

Quantitative diastereomeric yields were obtained from samples with R:S ratios as low as 80:20.[17] Monomers of 61:39 composition gave diastereomeric excesses of 85 to 94% in different trials. However, at 60:40 the optical yield began to drop dramatically, reaching a value of 0 for a 50:50 mixture. Apparently crystals of both chiralities were present in large amounts in this region of composition.

Similar results were obtained for optically pure samples of the α form of 10.[18] However, irradiation of a second, β form of the R isomer gave cyclobutane rings of SSSS configuration while the S isomer gave RRRR rings. Only the structure of the β form has been determined, but since the reactivity of the α form is similar to that of 8, comparison of the packing of 8 with that of the β form of 10 may explain the unusual results. Such a comparison (Figure 1) indicates that the diene systems of the α and β forms

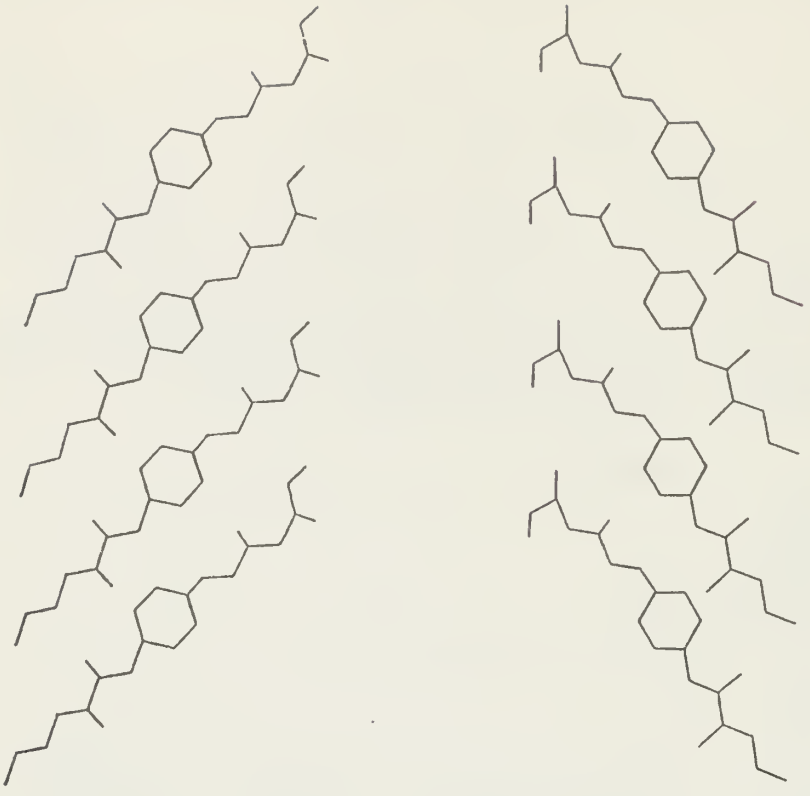
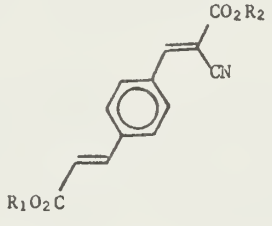


Figure 1. (a) Packing of the β form of 10. (b) Packing of 8.

are enantiomeric, but the secondary-butyl groups assume different orientations in the two forms. This difference could explain the opposite effect on crystal chirality of the α and β forms.

The packing of 8 was examined in order to choose achiral analogues. The intermolecular contacts involving the secondary butyl group were studied to determine what replacements could be made without disturbing the packing arrangement that leads to chiral products. Compounds 12-18 were chosen for examination.[19]



12	R_1 = isopropyl	R_2 = ethyl
13	R_1 = 3-pentyl	R_2 = ethyl
14	R_1 = 0.5 isopropyl, 0.5 3-pentyl	R_2 = ethyl
15	R_1 = isopropyl	R_2 = n-propyl
16	R_1 = 3-pentyl	R_2 = methyl
17	R_1 = t-butyl	R_2 = ethyl
18	R_1 = 3-pentyl	R_2 = n-propyl

Of the above dimers, 14, 16, and 18 formed chiral crystals. Photodimerization of each compound gave optically active products. In order to determine the enantiomeric excess in those experiments, mixed crystals

(12:8 30:70, 13:8 60:40 and 16:8 25:75) were prepared and structural similarity to crystals of 8 was established by powder photographs. Irradiation of each mixed crystal gave the three possible products in statistical distributions. Dimer 9 (homodimer of 8) was isolated from each product mixture and found to be optically pure by the previously mentioned NMR technique. Other resulting dimers were assumed to be optically pure and their specific rotations were determined. By comparison with those specific rotations, the enantiomeric excesses were found to range from 3 to 6% in the dimerization of 14 and from 44 to 100% in the case of 16. The values were checked by transesterification of the dimers to the tetramethyl ester, which could then be compared with a sample made from similar treatment of optically pure 9. These dimerizations were carried out on single crystals.

Large enantiomeric excesses were also obtained from polycrystalline samples as a result of autoseeding. The influence of the initially formed crystal causes an excess of crystals of the same chirality to form. A preference for either enantiomeric form is equally probable in a given experiment.

A more reliable method to crystallize an excess of one enantiomeric modification of monomer crystals was developed. This involved crystallization of monomers in the presence of optically pure dimers.[20] Since the effect of crystal chirality on the stereochemistry of the reaction had been previously established, optical yields of the photodimerization of the resulting crystals were used to evaluate the success of the crystallization procedure.

Crystals of 14, 16, and 18 were grown from the melt and from solution in the presence of small amounts (0.05-15% (w/w)) of optically pure dimer 9. Irradiation of monomer crystals grown with dimers of SSSS configuration gave cyclobutanes of RRRR configuration. Conversely, use of RRRR additives led to an excess of SSSS dimers. The enantiomeric excess varied from 35 to 100%. Crystallizations in different solvents and at different temperatures changed only the magnitude of the effect.

The proposed mechanism of the crystallization involves preferential adsorption of the dimer. A chiral dimer is structurally similar to monomer stacks in crystals of the form that leads to dimers of the same chirality. The dimers are then preferentially adsorbed on the surface of those crystals, decreasing the rate of growth. Crystals of opposite chirality are unaffected and thus will be formed in excess. Success of the method in other systems depends upon the choice of a structurally similar additive.

This mechanism is supported by the observation that the amount of additive incorporated in the crystal (approx. 0.5%) is close to the minimum concentration needed for maximum asymmetric induction. It was also shown that the results depend on the chirality of the cyclobutane ring in 9 and not of the secondary butyl group.

This crystallization method has also been used to resolve racemic mixtures of amino acids.[21] The effect could also be used as an empirical method for the determination of absolute configuration. The involvement of similar processes in the origination of optical activity on earth has even been suggested.[22]

In conclusion, the study of photodimerizations demonstrates that greater selectivity can sometimes be achieved by running a reaction in the solid

state. However, the synthetic utility of such reactions is limited, since molecules cannot always be made to crystallize in the desired orientations.

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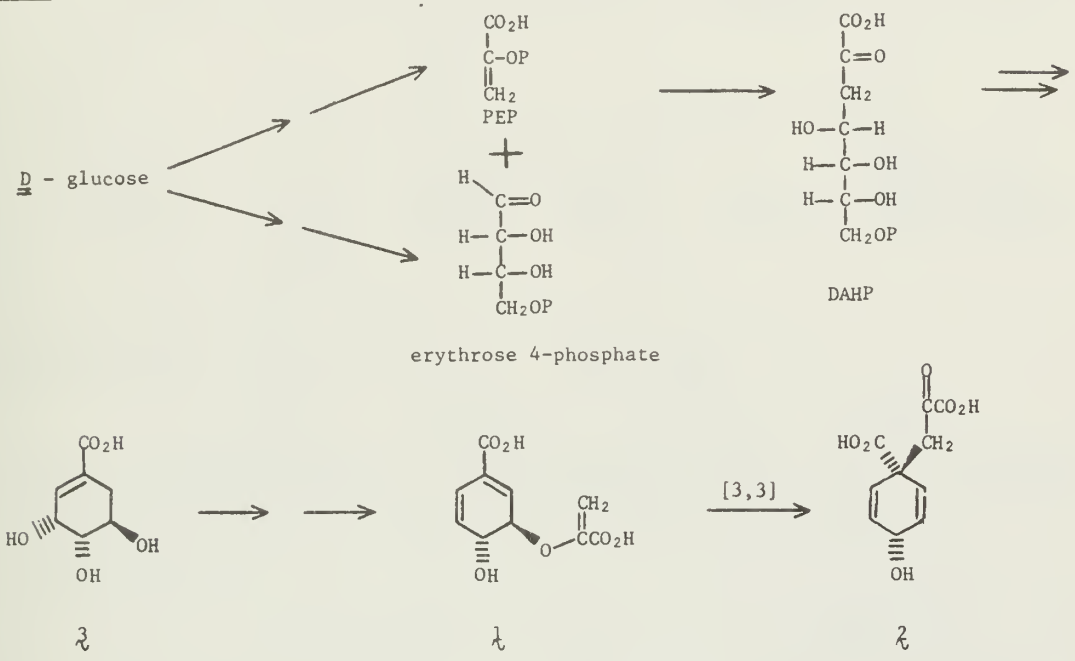
RECENT SYNTHESES OF INTERMEDIATES ON THE SHIKIMIC ACID PATHWAY

Reported by Terence Moran November 14, 1983

Introduction

The shikimic acid pathway (Scheme I) proceeds through a series of common alicyclic intermediates: chorismic acid (1), prephenic acid (2), and shikimic acid (3). These three intermediates lead to ubiquitous and

Scheme I



essential natural products (Table I).[1] Shikimic acid (3) also results in

Table I

last shikimic acid pathway intermediate	more immediate precursor	natural product	functions
chorismic acid	o-aminobenzoic acid	tryptophan	essential amino acid
	p-aminobenzoic acid	folic acid	coenzyme in nucleotide synthesis
	o-succinylbenzoic acid	naphthoquinones, anthraquinones	vitamins K
prephenic acid	phenylpyruvic acid	phenylalanine	essential amino acids
	arogenic acid	tyrosine	
shikimic acid	coniferyl alcohol	lignins	structural polymers in wood

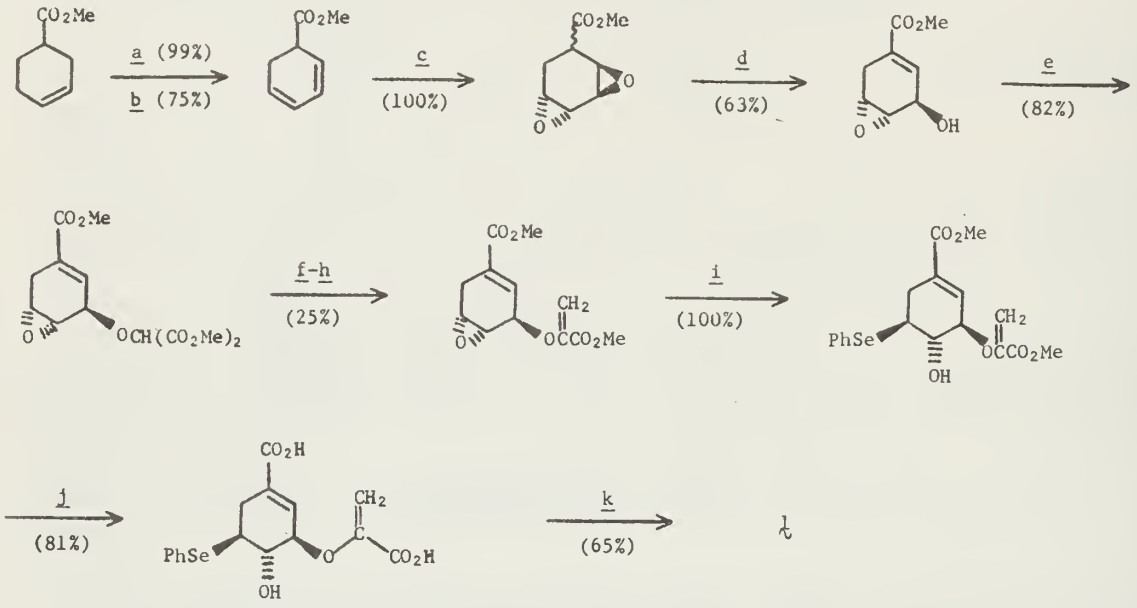
biologically active natural products containing the meta-C_7N unit (i.e., m-toluidine), such as geldanamycin and mitomycin C.[2d,b] The aim of this seminar is to report total syntheses, structure determinations, and labelling studies of chorismic acid (1), prephenic acid (2), and shikimic acid (3) which have been reported since Ganem's review.[3] Syntheses of chorismic acid (1) and prephenic acid (2) were reported only recently; earlier efforts were frustrated by the extreme lability of these compounds.[4-10] Notably, the [3,3]sigmatropic Claisen rearrangement of 1 to 2 proceeds rapidly in vitro

(half life of 1 at 70°C and pH 8 = ca. 30 min) and kinetic studies reveal that chorismate mutase accelerates this rearrangement at 37°C by a factor of 1.9×10^6.[3] Also, loss of pyruvate from 1 results in p-hydroxybenzoic acid. If chorismic acid (1) were not so labile, its importance as the key branchpoint intermediate might have resulted in the phrase "chorismic acid pathway."

Chorismic Acid

The original isolation and structure determination, as well as two recent syntheses of 1,[4-6] were complicated by its extreme lability. Immediately prior to the preparation of this abstract, Berchtold reported an improved synthesis of 1 in 6% total yield (Scheme II).[4] By contrast,

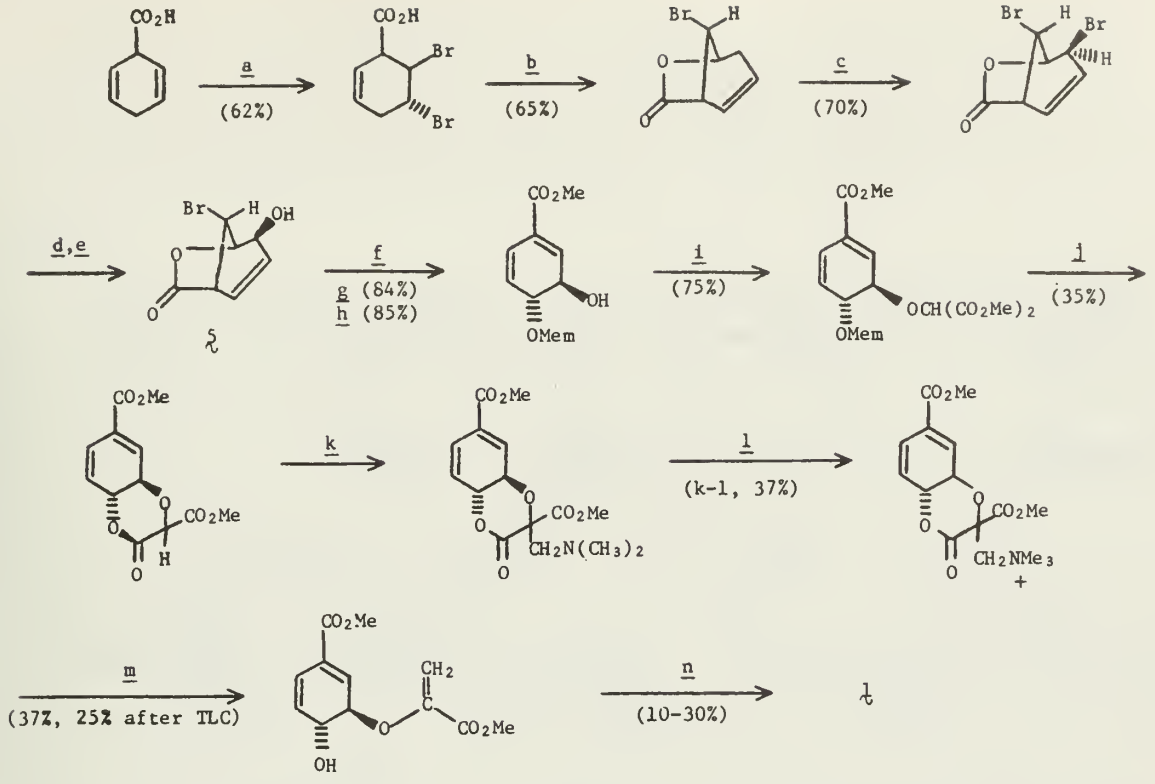
Scheme II.



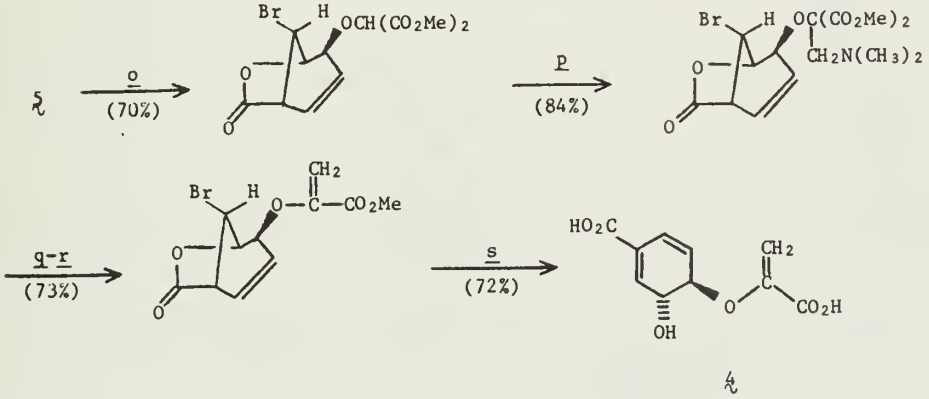
a) 2eq. NBS/AIBN; b) 2eq. $(n\text{-Bu})_3SnH$/AIBN; c) 2eq. m-CPBA; d) DBU; e) $N_2C(CO_2Me)_2$, $Rh_2(OAc)_4$; f) $(CH_3)_2N^+{=}CH_2I^-$; g) CH_3I; h) DMSO, 80°; i) Ph_2Se_2, minimal $NaBH_4$ to decolorize; j) NaOH/THF-H_2O; k) 3eq. H_2O_2, 3.5-dimethoxyaniline.

Berchtold's original synthesis and Ganem's synthesis afforded 1 in ~0.2% yield.[5,6] A key modification of Berchtold's earlier route was hydrolysis of the two ester moieties before selenoxide elimination, using 3,5-dimethoxyaniline as a PhSeOH scavenger to avoid aromatization. Another modification that improved the yield was the attachment of the malonate moiety using dimethyl diazomalonate and catalytic $Rh_2(OAc)_4$. Ganem's synthesis (Scheme III) afforded pseudochorismic acid (4) in addition to 1.[6] The bicyclic intermediate 5, useful in the synthesis of 6β-deuterioshikimic acid (3a) described later,[11] was prepared from 1,4-dihydrobenzoic acid.[12a,b] One major obstacle was attachment of the enol pyruvate side chain. Formation of the Mannich base from the malonate with Eschenmoser's salt was only possible in the pseudochorismate case, due to aromatization probably initiated by iodide attack on the ring. The problem was avoided by using Potier's salt $[CH_2{=}N^+(CH_3)_2\ CF_3CO_2^-]$, which afforded a 4:1 mixture of Mannich base and methyl m-enolpyruvylbenzoate.

Scheme III.



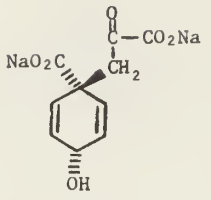
a) Br_2; b) $NaHCO_3$; c) NBS; d) 4eq. NaOAc/HMPA; e) H_2SO_4/THF; f) $MeO(CH_2)_2OCH_2\overset{+}{N}Et_3Cl^-$; g) 2eq. KOH/THF; h) MeI/HMPA; i) 1.2eq. $N_2C(CO_2Me)_2$, $Rh_2(OAc)_4$; j) p-TsOH; k) $CH_2{=}\overset{+}{N}(CH_3)_2CF_3CO_2^-$; l) FSO_2OCH_3; m) 1.5eq. NaOH/H_2O, prep. S_iO_2 TLC/5°C; n) NaOH/THF-H_2O/0°C.



o) $N_2C(CO_2Me)_2$, $Rh_2(OAc)_4$; p) $CH_2{=}\overset{+}{N}(CH_3)_2I^-$; q) CH_3I; r) Me_2SO/Δ; s) NaOH/THF-H_2O.

Prephenic Acid

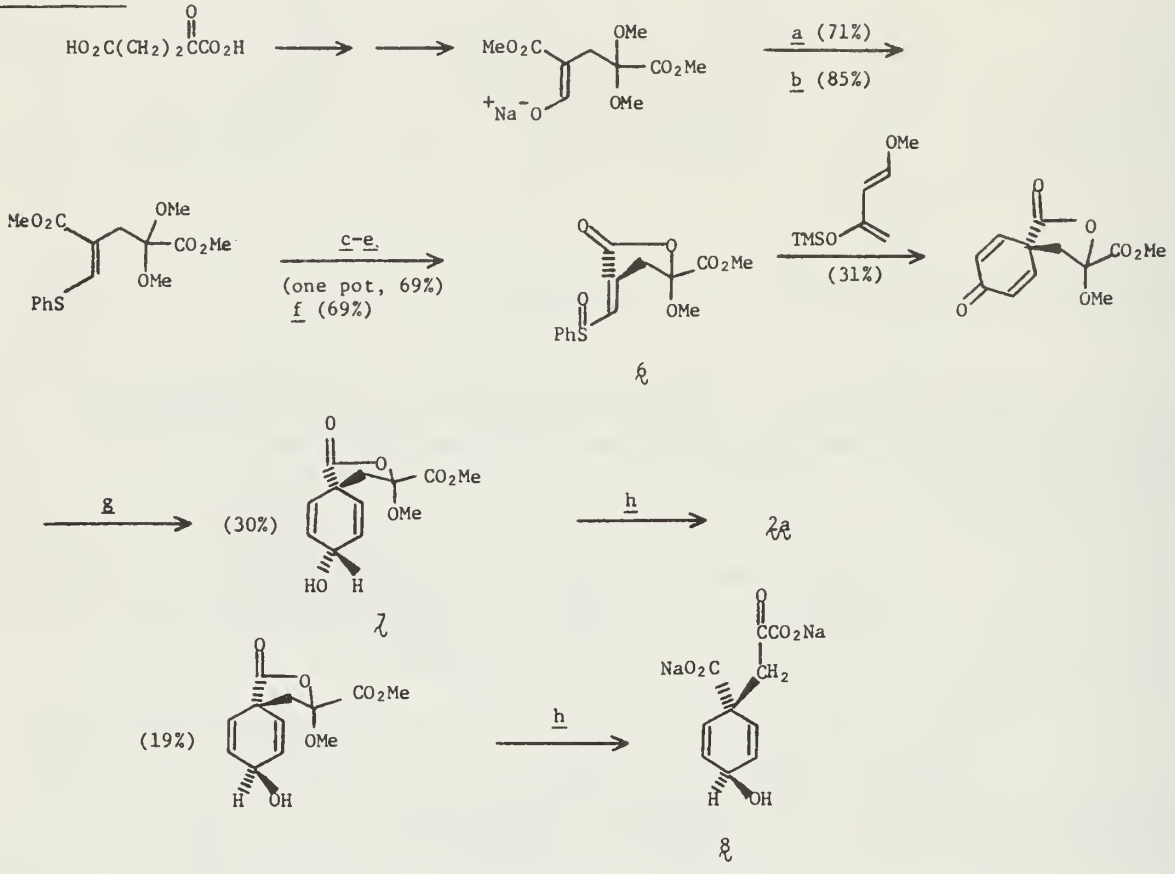
Prephenic acid (2) is extremely labile to acid catalyzed decomposition to phenylpyruvate, which excludes acetal protection of the α-keto acid functionality as the acetal. The free acid (2) is unstable and the two syntheses and structure determinations described refer to the disodium salt (2a). Danishefsky's approach to the synthesis of 2a avoids acid-removed acetal protection and the corresponding undesired acid-catalyzed aromatization by forming lactone 6.[7,8] This intramolecular protection stored both α-keto and



2a

carboxy functions, which could then be released under the desired alkaline conditions at a later step (Scheme IV). The starting material was prepared

Scheme IV.



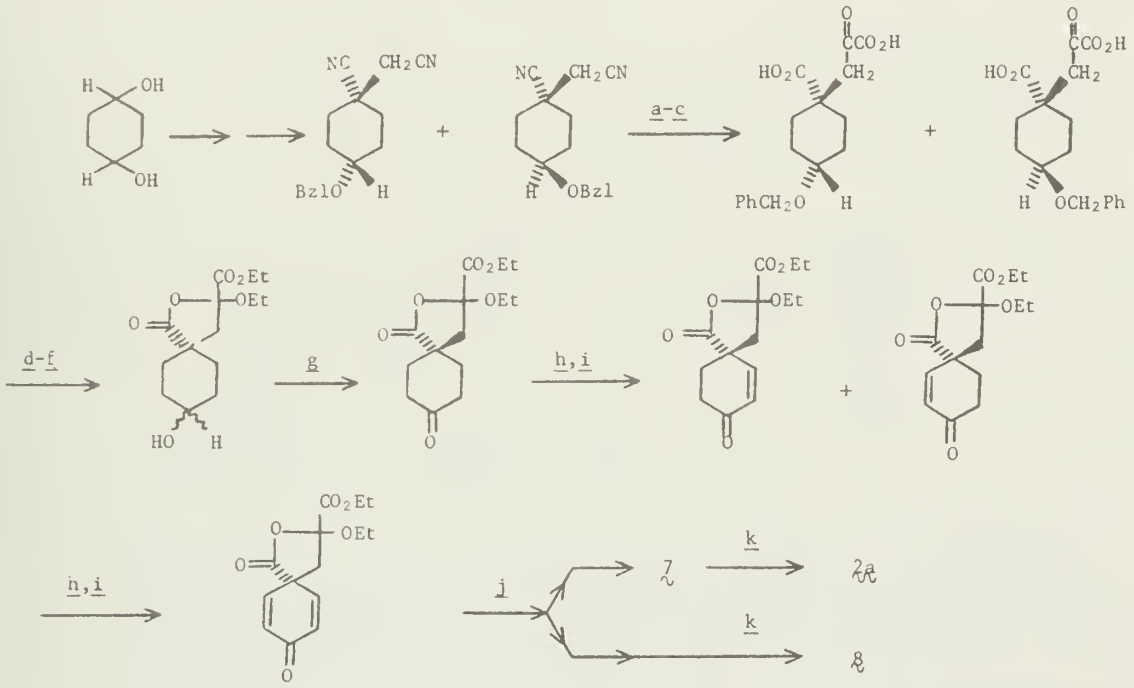
a) TsCl; b) PhSNa/pyr; c) 5eq. KOH; d) .012N HCl/THF; e) CH_2N_2; f) m-CPBA; g) 9-BBN/THF/0°; h) 1.25eq. NaOH/MeOH-H_2O.

previously by Plieninger from 2-oxoglutaric acid.[13] The three-step intramolecular protection was carried out in one pot to increase yields of the resulting lactone which was then caused to react with the Danishefsky diene neat in a sealed tube to afford crude dienone in 70-80% yield. Unfortunately, the inefficiency of crystallization resulted in a loss of material (31% isolated yield). The most specific reducing agent was 9-BBN. The NMR spectrum showed the desired dienol stereoisomer 7 to be in preponderance (3:1), but instability on silica gel resulted in the loss of ~50% of the desired stereoisomer 7 and a 3:2 ratio of products. Treatment of 7 with NaOH in methanol afforded 2a, identical with the salt obtained from ion exchange of barium prephenate from natural sources. Disodium epiprephenate (8) was obtained by an identical procedure. The stereochemistry of prephenate was rigorously confirmed by X-ray crystal structure determination

of 7, the immediate precursor to 2a.

Plieninger has also completed an independent total synthesis of 2a and confirmation of the stereochemical structure by an unambiguous chemical route.[9,10] The final two steps were identical to the Danishefsky route, namely 9-BBN reduction to obtain a prephenate-epiprephenate mixture in a 4:3 ratio, followed by basic unmasking of the two lactone-protected groups. However, the approach leading up to 7 was different (Scheme V). The

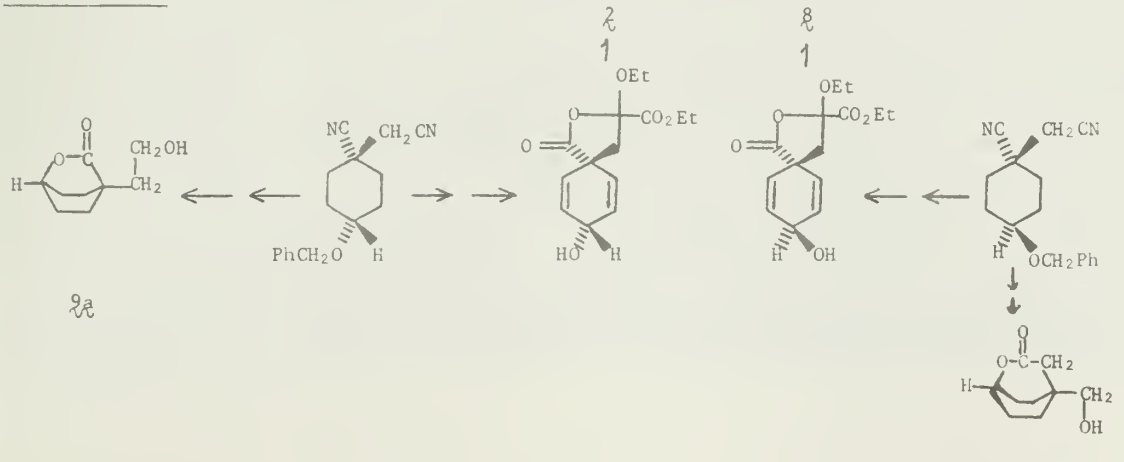
Scheme V.



a) $(CO_2Et)_2$, KOEt; b) HCl, H_2O; c) H_2SO_4; d) C_6H_6/Δ; e) EtOH, H^+; f) Pd/C, H_2; g) H_2SO_4, K_2CrO_7; h) PhSeCl; i) H_2O_2; j) 9-BBN; k) MeOH, NaOH, H_2O.

lactone acetal was formed under acidic conditions in this case also, but manipulations were done on a six-membered ring that already existed in the diol starting material. The dienone was formed from the corresponding ketone by two successive selenoxide eliminations. Confirmation of the structure was be chemical means (Scheme VI). Compounds 9a and 9b had the same precursors as 2 and 8, respectively, and could be distinguished much more easily by clear assignments in their ^1H NMR spectra.

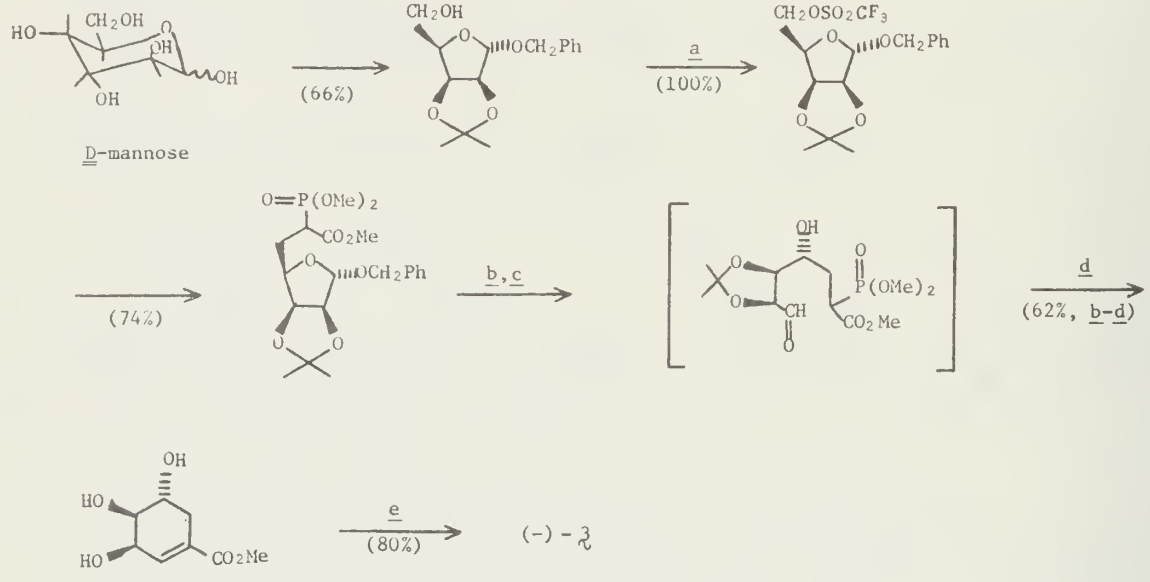
Scheme VI.



Shikimic Acid

Several syntheses of shikimic acid (3) appeared during the sixties,[1,3] and this material is available from Aldrich [$20/g]. Although 3 has an additional chiral center compared with 1, it is less labile to aromatization and rearrangement. A short, efficient, and enantiospecific synthesis of (-)-shikimic acid (3) was reported by Fleet (Scheme VII) using carbohydrate as starting material as a chirality source.[14] In this way, it resembles

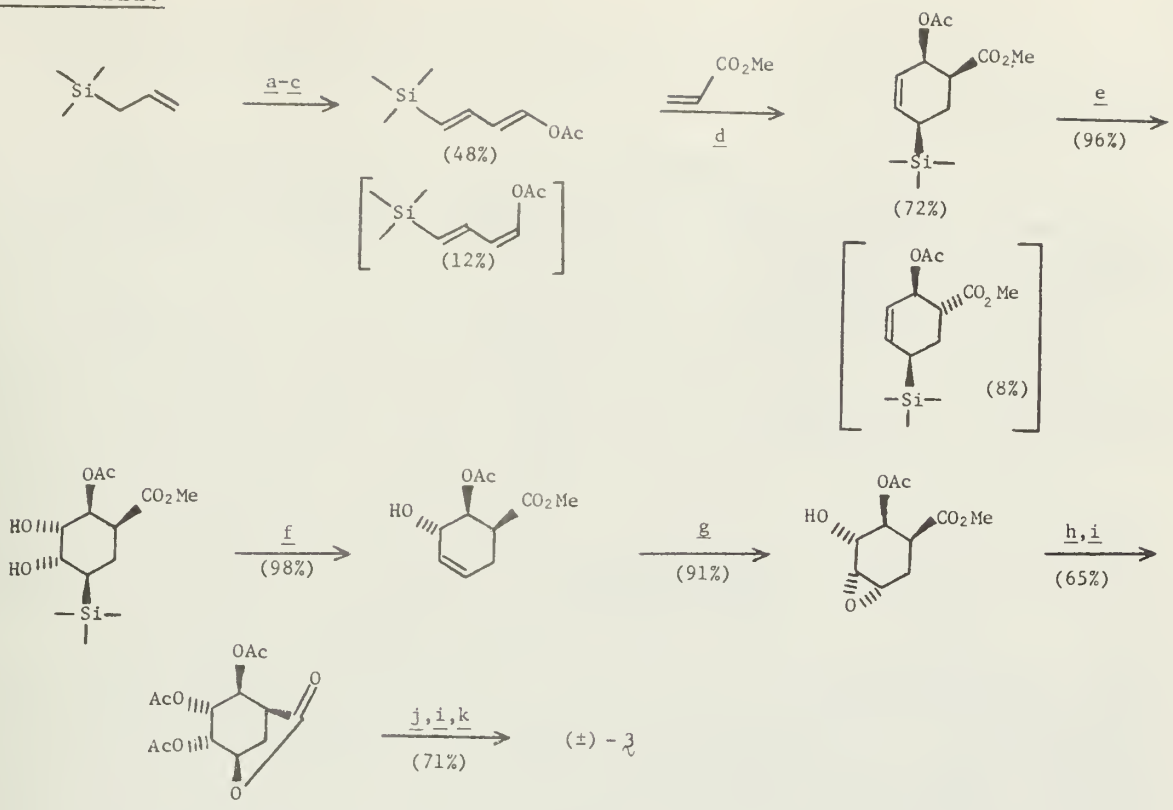
Scheme VII.



a) $(F_3CSO_2)_2O$; b) Pd/H_2; c) 3eq. NaOMe; d) Dowex 50-W X-8 resin/H^+, MeOH; e) alkaline, H_2O.

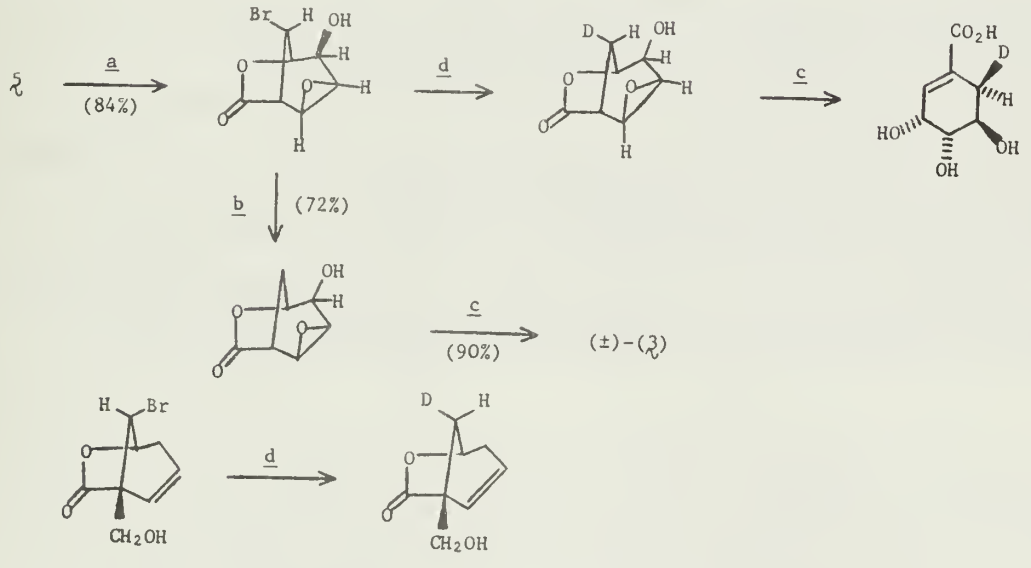
the biosynthesis (Scheme I), wherein DAHP is the precursor. The key step was the intramolecular Wadsworth-Emmons olefination (62%). The overall yield was 25% in five steps. Allylsilane methodology (Scheme VIII) was applied to the synthesis of racemic 3 by Koreeda.[15] The separation of dienes was unnecessary because the minor undesired isomer did not react in the succeeding Diels-Alder reaction and was recovered easily. The crucial step involves oxidative desilylation of the allylsilane Diels-Alder product. Direct epoxidation-desilylation proved unsuccessful with a number of peracids under a variety of conditions. Facile stereospecific conversion into the allylic alcohol could be achieved in a two-step procedure (94%) via the cis-diol (Upjohn procedure) and p-TsOH-catalyzed elimination of the trimethylsilyl-hydroxy unit. Introduction of the 3β,4α-diol system was also difficult because acid hydrolysis of the epoxide led to three triols. In contrast, treatment of the epoxide with LiOH followed by acetylation afforded the γ-lactone triacetate directly. Although the yield (14%) was not as high as in the Fleet approach (25%), one attractive advantage is that the use of ^{13}C-labelled N,N-dimethylformamide to produce the diene would result in the introduction of a ^{13}C-label at C-2 or 3. Ganem's synthesis (Scheme IX) of 3 also utilized bicyclic allylic alcohol 5 (Scheme III) as the starting material.[11] The overall yield was only 13%, but an attractive aspect is the possibility of forming 6β-deuterioshikimic acid. The Bu_3SnD reduction gave retention in one system and inversion in another related system (Scheme IX), which implies that the transition radi-

Scheme VIII.



a) sec-BuLi/TMEDA; b) DMF; c) Ac_2O; d) xylene (reflux); e) OsO_4, N-methylmorpholine N-oxide/t-BuOH, acetone; f) p-TsOH; g) mCPBA; h) LiOH/THF-H_2O; i) Ac_2O, Py; j) HCl gas/MeOH; k) DBU/THF.

Scheme IX.



a) CF_3CO_3H; b) Bu_3SnH/AIBN; c) KOH; d) Bu_3SnD.

cal corresponding to the observed stereochemistry is more stable. The stereochemistry of all compounds were assigned via 300 MHz ^1H NMR decoupling experiments.

Summary

The seven recent syntheses of intermediates on the shikimic acid pathway reported since 1978 can be summarized in Table II.

Table II

target compound	research director	year(s) reported	yield, %	ref.
chorismic acid	G. Berchtold	1982, 1983	6	4,5
	B. Ganem	1982	0.2	6,12
disodium prephenate	S. Danishefsky	1977, 1979	---	7,8
	H. Plieninger	1978, 1979	---	9,10,13
(-)-shikimic acid	G. Fleet	1983	25	14
(±)-shikimic acid	M. Koreeda	1982	14	15
	B. Ganem	1982	13	11,12

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THE USE OF PENTAVALENT ORGANOBISMUTH COMPOUNDS IN ORGANIC SYNTHESIS

Reported by Dean Hoglen November 17, 1983

A continuous search for oxidizing agents that can avoid pH and temperature extremes detrimental to the varied functional groups introduced in the course of natural product synthesis has resulted in exploration of the oxidizing ability of the Bi(V)-Bi(III) change of pentavalent organobismuth compounds.[1,2] The large number of pentavalent triarylbismuth derivatives with suitable solubility properties and easy synthetic access has also made exploration of the oxidative abilities attractive.[2,3] Rigorously anhydrous conditions are unnecessary, and a large excess of reagent is not required as in oxidations using, for example, manganese dioxide, silver carbonate on celite, and chromium trioxide-pyridine.[1,2,4-6] The use of chromium-based reagents can also result in oxidative cleavage products, as in the oxidation of a secondary alcohol that gives an alcohol and aldehyde as well as the expected ketone.[2,7] Exploration of the properties of pentavalent bismuth has resulted in new reagents for oxidation of alcohols, cleavage of glycols, and arylation of ketones, phenols, and diols.

Inorganic bismuth compounds had been used previously as oxidants. Sodium bismuthate cleaves glycols to give aldehydes in acidic aqueous solution at room temperature.[1,2,8] Acyloins are oxidized to 1,2-diketones by bismuth trioxide (Bi_2O_3) in solutions containing acetic acid.[2,9] The first reported oxidation using an organobismuth compound involved triphenylbismuth dihydroxide, an unstable compound prepared from the reaction of triphenylbismuth dichloride with aqueous silver oxide, that oxidized ethyl, n-propyl, and isopropyl alcohols to acetaldehyde, propionaldehyde, and acetone, respectively, isolated as their 2,4-dinitrophenylhydrazone derivatives.[2,10]

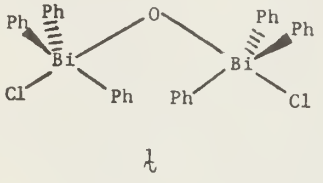
Structure of Pentavalent Bismuth Compounds

The structures of several pentavalent organobismuth compounds have been studied and found to be distorted trigonal bipyramids. Organobismuth compounds of the type Ph_3BiX_2 where X is a halide, acetate, or nitrate have been shown to be non-ionic and monomeric from molecular weight, conductance, and infrared data.[11] The crystal structure of triphenylbismuth dichloride is a distorted trigonal bipyramid with the electronegative chlorine atoms in the apical positions and the phenyl groups in the equatorial positions.[12] The structure of μ-oxo-bis(perchloratotriphenylbismuth(V)), $(Ph_3BiClO_4)_2O$, was also elucidated by X-ray crystallography and found to consist of distorted trigonal bipyramids at the bismuth atoms with the bridging oxygen and the perchlorates apical and the phenyl groups equatorial.[13] Divalent oxy-anions such as triphenylbismuth carbonate are non-ionic polymeric structures with bridging anion groups.[14]

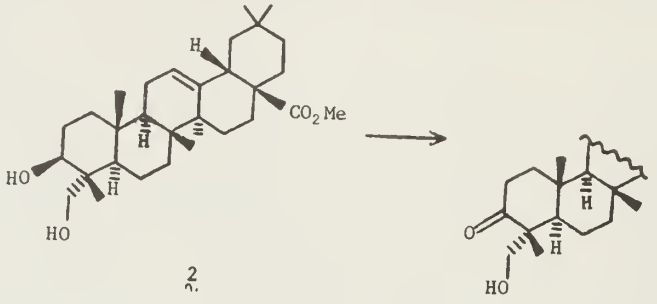
The apical location of the more electronegative ligands could be predicted from the basic theory of hypervalent bonds. Bismuth's bonding with its apical ligands must be a hypervalent three-center four-electron bond involving a filled orbital of the central bismuth atom and a valence electron from each of its apical ligands.[15,16] The resulting bond has excess electron density on the apical ligands due to the node in the nonbonding orbital, resulting in a preference for electronegative ligands. The nature of the bond and the preference for electronegative ligands play a significant role in the chemistry of pentavalent organobismuth compounds as oxidant and phenylating agent.

Pentavalent Organobismuth as Oxidant

More than forty years after the first isolated report of an organobismuth oxidation, Barton began studies using the triarylbismuth derivative μ-oxo-bis(chlorotriphenylbismuth) (1) prepared from the reaction of triphenylbismuth dichloride with alcoholic sodium hydroxide.[1,17] Compound 1



1



2

was chosen for study because of its solubility in the commonly used organic solvents dichloromethane, chloroform, and benzene.[1] The usual oxidation procedure involved mixing a 1:1.25 molar ratio of the reagent and alcohol in dichloromethane with a molar excess of K_2CO_3 or $NaHCO_3$ and stirring the mixture until reaction was complete. The pentavalent organobismuth reagent proved to be an effective oxidant of many hydroxy-containing compounds under mild pH conditions and usually at room temperature (Table I). It is especially effective in the oxidation of allylic alcohols, giving high yields. The oxidative method avoids overoxidation of primary alcohols to carboxylic acids, formation of esters from primary alcohols, and rearrangement and cleavage of double bonds, all common in oxidation with chromic acid in acidic solution.[18] Allylic alcohols are oxidized without excess reagent and in shorter times than with manganese dioxide.[18] In the oxidation of methyl hederagenin (2) a significant improvement was made in the yield of the 3-oxo product over the oxidation with potassium permanganate.[1]

Table I

Oxidation by μ-oxo-bis(chlorotriphenylbismuth)[1]

alcohol	time,h	temp,°C	base	product	yield,%
cinnamyl alcohol	15	21	K_2CO_3	cinnamaldehyde	83
cholest-4-en-3β-ol	6	21	K_2CO_3	cholest-4-en-3-one	89
(-)-carveol	6	21	K_2CO_3	carvone	84
benzyl alcohol	15	21	K_2CO_3	benzaldehyde	82
1-pentanol	6	60	$NaHCO_3$	Pentanal	79
cholestanol	30	21	K_2CO_3	cholestanone	75
cholestane-3β,6β-diol	15	21	K_2CO_3	cholestan-3β-ol-6-one	50
				cholestan-3,6-dione	25
methyl hederagenin	24	21	K_2CO_3	methyl hederagonate	36

Barton's work was expanded to include other triaryl derivatives of bismuth.[19] Competitive reactions for allylic alcohol involving 1:1 mixtures of $Ar^1_3BiCl_2$ and $Ar^2_3BiCl_2$ showed an increase in the relative rate of reaction through the series: p-tolyl, phenyl, p-chlorophenyl of 1:1.5:6, indicating that electron-withdrawing substituents accelerated the oxidation. Variation in the leaving group X in Ph_3BiX_2, however, had no detectable effect on the reaction rate when X was Cl, Br, or ONO_2. When $NaHCO_3$ or K_2CO_3 was replaced by pyridine or collidine there was a loss of oxidizing power, and it was therefore concluded that the active oxidant in the reaction mixtures was triarylbismuth carbonate. The dichloride reacted with potassium carbonate in aqueous acetone to give triphenylbismuth carbonate, isolated

as an amorphous solid. It was an effective heterogeneous oxidant in dichloromethane for several functional groups, showing at the same time remarkable selectivity (Table II).

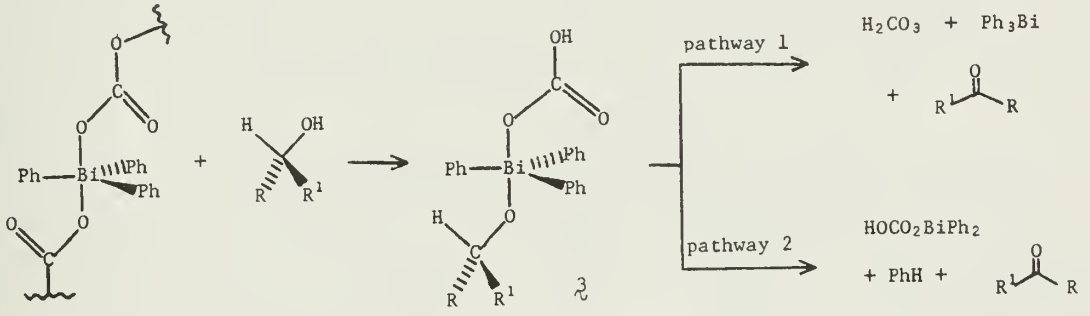
Table II

Oxidation by triphenylbismuth carbonate[19]

substrate	time,h	temp,°C	product	yield,%
(-)-carveol	1.5	40	(-)-carvone	84
cholest-4-en-3-ol	18	r.t.	cholest-4-en-3-one	97
meso-hydrobenzoin	1.5	40	benzaldehyde	97
$Ph_2C{=}NNH_2$	5	r.t.	Ph_2CN_2	97
PhNHNHPh	1.5	r.t.	PhN=NPh	90
$PhNHNHCPh_3$	4	r.t.	$PhN{=}NCPh_3$	95
5α-cholestan-3-one oxime	15	r.t.	5α-cholestan-3-one	60

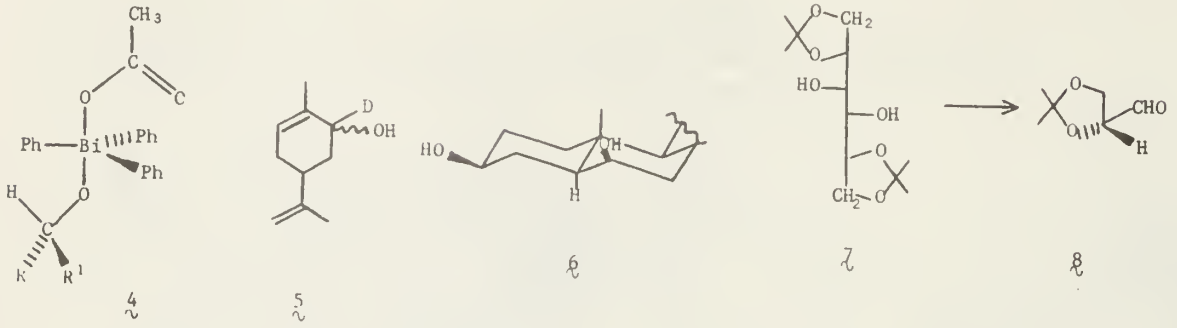
The proposed reaction sequence for alcohol oxidation involves the initial formation of an intermediate, 3, expected to have trigonal bipyramid geometry with the more electron withdrawing substituents occupying apical positions.[20] The operation of more than one mechanistic pathway in the breakdown of intermediate 3 was suggested by the observation that only 50%

Scheme I.



triphenylbismuth could be isolated after the oxidation of (-)-carveol to carvone in 84% yield.[20] Similar discrepancies in the molar ratio of product to triphenylbismuth were observed in the oxidation of other alcohols. Barton concluded that an intermediate could break down by the two pathways shown in Scheme I. Reactions were next carried out to determine the exact nature of the side products formed in the oxidations. Triphenylbismuth diacetate was used instead of triphenylbismuth carbonate so that the reaction mixture could be kept homogeneous; the base tetramethylguanidine was added to assist in the removal of the hydroxyl proton to form 4. The oxidation of the allylic alcohol (-)-carveol by triphenylbismuth diacetate in the presence of tetramethylguanidine was monitored by NMR spectroscopy in deuteriochloroform, and the gradual formation of a benzene peak at δ7.24 was observed. Reaction of tri-p-tolylbismuth dibenzoate with deuteriocarveol (5) in tetralin using 1,5-diazabicyclo[5.4.0]undec-5-ene as the base gave monodeuteriotoluene. An analogous reaction using tri-p-methoxyphenylbismuth carbonate gave p-deuterioanisole. These observations suggest the intramolecular transfer of a proton from the alcohol to a phenyl ring in pathway 2 as the ketone is formed. Attempts to trap free aryl radicals using nitrosobenzene or nitrosomesitylene failed, indicating "free" radicals are not involved in either mechanistic pathway. The oxidation of the more sterically hindered 6β-OH group in cholestane-3β,6β-diol (6) is consistent with the breakdown of intermediate 3 as the rate determining step. It would be possible to determine whether the transfer of the proton geminal with the hydroxyl group of the alcohol is involved in the rate

determining step from the relative rate of oxidation of 5 versus non-deuterated carveol, as in Westheimer's study of the oxidation of 2-propanol by chromic acid.[21]



4 5 6 7 8

Triphenylbismuth carbonate also proved useful for glycol cleavage.[19] In the cleavage of meso-hydrobenzoin, essentially quantitative recovery of triphenylbismuth was observed, which contrasted sharply with the previously stated observation that in the oxidation of (-)-carveol to carvone in 84% yield, only 50% triphenylbismuth was recovered. Barton was able to set up a catalytic cycle for glycol cleavage using N-bromosuccinimide or N-bromoacetamide for oxidation of triphenylbismuth in the presence of potassium carbonate and a small amount of water.[22] The aldehyde and/or ketone products of cleavage were obtained in good to excellent yields using only one percent triphenylbismuth, in the absence of which no glycol cleavage occurred (Table III). 1,2:5,6-Di-O-isopropylidene-D-mannitol (7) gave

Table III

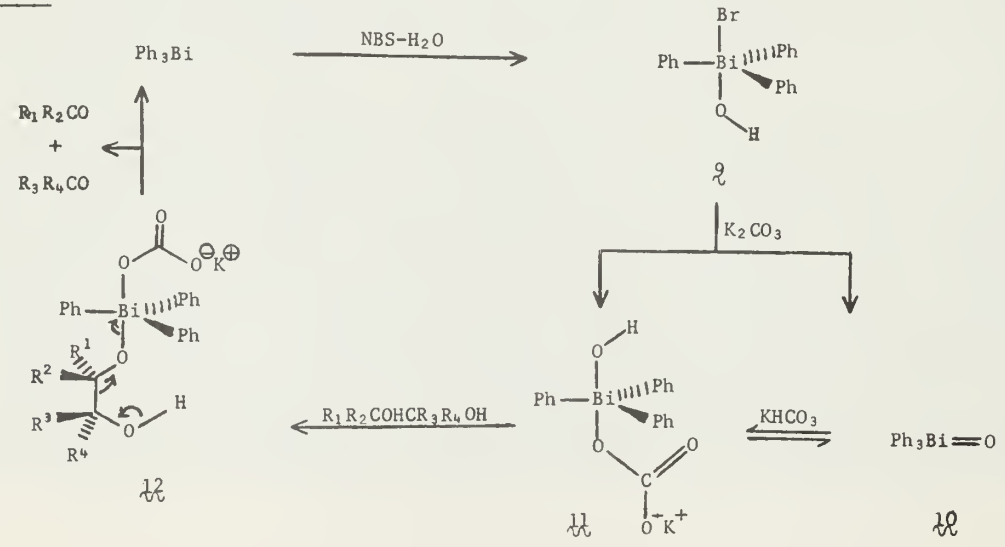
α-Glycol cleavage catalyzed by triphenylbismuth[22]

diol	Ph_3Bi, equiv.	time, min.	product	yield, %
$(CH_3)_2C(OH)C(OH)(CH_3)_2$	0.01	90	$(CH_3)_2CO$	100
$Ph_2C(OH)C(OH)Ph_2$	0.01	190	Ph_2CO	84
cis-cyclopentane-1,2-diol	0.01	90	pentane-1,5-dial	63
cis-decalin-9,10-diol	0.01	360	cyclodecane-1,6-dione	68
trans-decalin-9,10-diol	0.01	360	cyclodecane-1,6-dione	54
dibenzyl L-tartrate	0.01	90	benzyl glyoxylate	83

the useful chiral synthon 2,3-O-isopropylidene-D-glyceraldehyde (8) without racemization.

The quantitative recovery of triphenylbismuth indicated to Barton that a single pathway was involved in the oxidative cleavage (Scheme II).[22] The

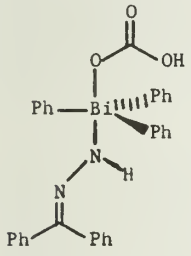
Scheme II.



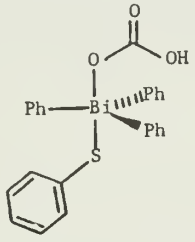
12 9 11 10

initial step is postulated to involve the formation of bromohydrin 9 from the reaction of triphenylbismuth with NBS and water. Triphenylbismuth does react with NBS and water in acetonitrile to give μ-oxo-bis(bromotriphenylbismuth). The bromohydrin reacts with the potassium carbonate to give triphenylbismuth oxide or its carbonate equivalent (11) which then forms the intermediate that breaks down to the products of oxidative cleavage. Intermediate 12 is thought to be not necessarily cyclic in nature, because cis decalin-9,10-diol is cleaved at about the same rate as rigid trans decalin-9,10-diol. For comparison, the selective rates of 100:1 were found for the cleavage of this pair of isomers by lead tetraacetate. It should be noted that periodate ion, frequently used in oxidative cleavage of glycols, does not cleave glycols that cannot form cyclic intermediates.[23]

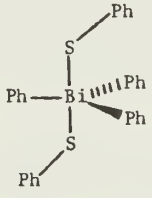
Triphenylbismuth carbonate was found to oxidize functional groups other than alcohols and glycols.[19] Benzophenone hydrazone was oxidized quantitatively to diphenyldiazomethane. No mechanistic work has been done; however, a reasonable reaction sequence could involve the formation and breakdown of the trigonal bipyramid intermediate 13, analogous to intermediate 3 in the oxidation of alcohols. This constitutes a promising general method of oxidizing hydrazones. The same oxidation by mercuric oxide requires a longer reaction time.[24] Manganese dioxide requires a large excess of oxidant and gives product contaminated with diphenylketazine. Aniline, dimethylaniline, pyrrolidine, indole, and 3-N-pyrrolidinocholesta-3,5-diene are unaffected by the oxidant, which should make triphenylbismuth carbonate useful in the oxidation of complex natural products compared with other oxidants, including chromic acid, manganese dioxide, permanganate, and lead tetraacetate that oxidize amines.[2,25] Thiophenol was oxidized to the disulfide by triphenylbismuth carbonate.[19] The formal mechanism could involve a nucleophilic displacement by thiophenol on intermediate 14 forming the protonated disulfide. Another possible intermediate is 15 formed from the exchange of the carbonates with two thiophenol molecules. The intermediate could break down to form the disulfide and triphenylbismuth. The



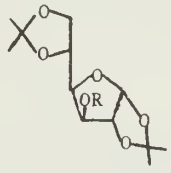
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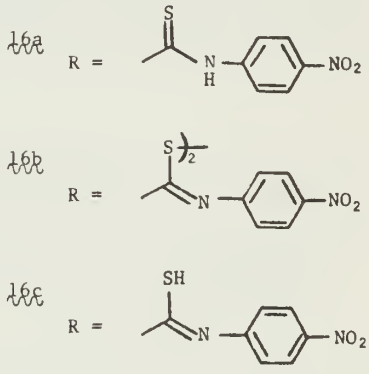
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15



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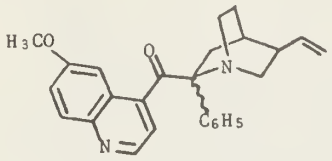


thiocarbonyl groups of xanthates. dialkylaminothionocarbamates and di-t-butylthioketone were not effected by triphenylbismuth carbonate although monoalkyl thionamide 16a was oxidized to disulfide 16b in 81% yield, presumably because 16a or, more likely, the tautomer 16c can react with the oxidant in the same manner as thiophenol.[20]

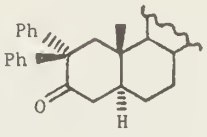
Pentavalent Organobismuth as Arylating Agent

Attempts to oxidize the alcohol quinine to the ketone quininone with triphenylbismuth carbonate gave a diasteriomeric mixture of the α-arylated ketone 17 in 75% yield and led to the discovery that triphenylbismuth carbonate could be used to phenylate ketones.[20] The potassium enolate

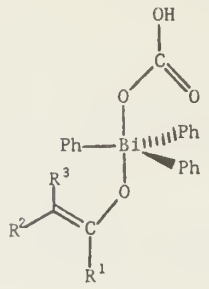
of cholestan-3-one reacted with triphenylbismuth carbonate to give 2,2-diphenylcholestan-3-one (18) (64%). Treatment of cyclohexanone with



17



18



19

an eightfold excess of potassium hydride followed by triphenylbismuth carbonate gave the highly sterically hindered 2,2,6,6-tetraphenylcyclohexanone in quantitative yield.[26] The mechanism proposed involves the formation of the enolic trigonal bipyramid derivative 19 which can undergo intramolecular arylation.[20]

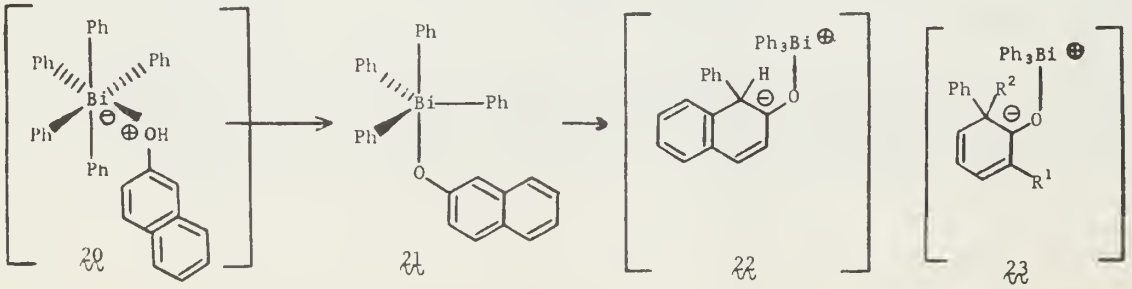
It was also found that triphenylbismuth carbonate would phenylate phenols; β-naphthol gave 1-phenyl-2-naphthol in 76% yield at room temperature in the presence of tetramethylguanidine.[20] The success of this reaction aroused interest in the use of other pentavalent organobismuth compounds, notably pentaphenylbismuth, the oxidizing and phenylating properties of which had been observed previously, and tetraphenylbismuth monotrifluoroacetate.[27,28] Pentaphenylbismuth was prepared by the reaction of triphenylbismuth dichloride with phenyllithium. Pentaphenylbismuth in dichloromethane or benzene reacted with 1-naphthol to give 2-phenyl-1-naphthol, notable in comparison with triphenylbismuth carbonate, which led to an intractable mixture of products. The use of pentaphenylbismuth has provided an easy route to 2,6-disubstituted-6-phenylcyclohexa-2,4-dienones, a group of compounds difficult to make using other synthetic methods (Table IV). The regiospecificity of pentaphenylbismuth for ortho arylation of phenols contrasts with aryllead(IV) triacetates which give significant amounts of both ortho and para arylated products.[29] In

Table IV

Phenylation by pentaphenylbismuth[27]

phenol	product	yield,%
2-naphthol	1-phenyl-2-naphthol	61
1-naphthol	2-phenyl-1-naphthol	48
2,6-dimethylphenol	6-phenyl-2,6-dimethylcyclohexa-2,4-dienone	72
2,3,5,6-tetramethylphenol	6-phenyl-2,3,5,6-tetramethylcyclohexa-2,4-dienone	82
p-nitrophenol	4-nitrophenyl phenyl ether	42

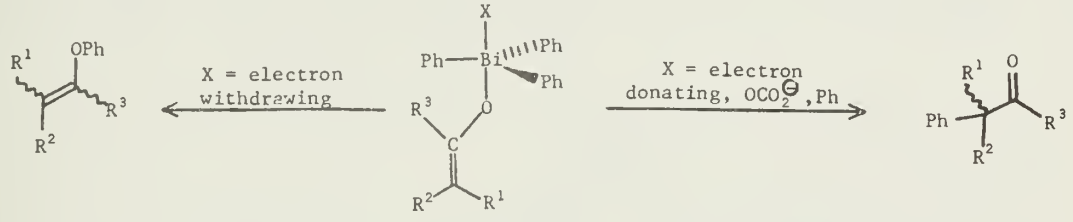
the arylation of phenols with pentaphenylbismuth, the reaction sequence will involve a series of intermediates. Attack by the phenol on pentaphenyl bismuth should form the octahedral 12-Bi-6 species (20) which should undergo proton transfer and loss of a benzene molecule to form the trigonal bipyramid intermediate. It could break down to form an intermediate 22 which should lose triphenylbismuth to form the keto form of the phenol which should tautomerize to the C-phenylated phenol. In the synthesis of 2,4-dimethyl-2,6-



20 21 22 23

diphenylcyclohexa-2,4-dienone from 2,4-dimethylphenol, 2,4-dimethyl-6-phenylphenol was shown to be an intermediate.[27] 2,4-Dimethyl-6-phenylphenol, as well as other 2,6-disubstituted phenols would form an intermediate 23 which cannot undergo proton transfer to reform a phenol, therefore forming instead a dienone.

The product differences in the reactions of pentaphenylbismuth and triphenylbismuth carbonate indicated quite simply that variation in the ligands attached to Bi(V) can alter the course of the reaction significantly. To extend understanding of the influence of the ligand, tetraphenylbismuth monotrifluoroacetate was prepared from the reaction of pentaphenylbismuth with trifluoroacetic acid in benzene.[30] It reacted with phenols to give O-arylation in good yield, thus providing a convenient synthetic route to aryl ethers. Reaction with the enolizable ketone dimedone gave the monoaryl enol ether in 55% yield (other products unspecified). The selective importance of the electron-withdrawing trifluoromethyl group was emphasized by the observation that tetraphenylbismuth acetate gave only the C-arylated product (40%).



24a X = $OCOCF_3$
24b X = Ph

The proposed mechanistic pathway for this reaction involves the formation of an intermediate, 24, the breakdown of which is profoundly affected by the electronegativity of the ligands. The breakdown of intermediate 24a gives O-phenylation, and a reasonable explanation for the formation of some C-arylated product in reactions of alcohols with tetraphenylbismuth trifluoroacetate is the formation of intermediate 24b which could follow the same reaction path described for pentaphenylbismuth.

The arylation of oxygen by Bi(V) compounds to form aryl ethers has been extended to diols.[32, 33] Although triphenylbismuth diacetate reacts with glycols in the presence of base to give oxidative cleavage products, it reacts with glycols to give monophenyl ethers in good yield under weakly acidic conditions in boiling dichloromethane using stoichiometric amounts of reagents (Table V). Notable features of the reaction are (1) mild conditions,

Table V

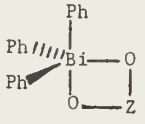
Phenylation by triphenylbismuth diacetate[33]

glycol	phenol ether	yield,%
CH_2OHCH_2OH	CH_2OHCH_2OPh	85
(±)-$CH_3CHOHCHOHCH_3$	$CH_3CHOPhCHOHCH_3$	86
$(CH_3)_2C(OH)C(CH_3)_2OH$	$(CH_3)_2COPhC(CH_3)_2OH$	15
$CH_2OHCH_2CH_2OH$	$CH_2OPhCH_2CH_2OH$	87
$CH_2OH(CH_2)_2CH_2OH$	$CH_2OPh(CH_2)_3CH_2OH$	80
$CH_2OH(CH_2)_3CH_2OH$	$CH_2OPh(CH_2)_3CH_2OH$	50
$CH_2OH(CH_2)_4CH_2OH$	$CH_2OPh(CH_2)_4CH_2OH$	40
cis-cyclopentane-1,2-diol	cis-2-phenoxycyclopentanol	41
trans-cyclopentane-1,3-diol	trans-2-phenoxycyclopentanol	51

(2) phenylation of hydroxyl group will occur only if another hydroxyl group is suitably located, and (3) there is a preference for axial hydroxyl groups in six-membered rings.

The need for two hydroxyl groups in a compound was easily demonstrated with cyclohexanol which gave at most 3% of phenoxycyclohexane after refluxing 24 hours in dichloromethane with triphenylbismuth diacetate. In sharp contrast, after refluxing for 4 hours in dichloromethane with triphenylbismuth diacetate, cyclohexane-1,2-diol was almost completely phenylated. 1,2-, 1,3-, and 1,4-diols gave practically the same yields, and yields of 1,5- and 1,6-diols were relatively good. The conclusion reached by David and Thieffry was that the phenylation of acceptor oxygen A involved another participant hydroxy group P. Steric requirements for A seem to be more severe than for P. Although a secondary hydroxyl group is easily phenylated in the presence of a tertiary hydroxyl group, ditertiary glycols are hard to phenylate, or, restated, a tertiary hydroxyl group is a poor phenyl acceptor.

David concluded that both hydroxyl groups must bond to the central bismuth atom displacing the acetate groups; however they must occupy positions that differ in steric requirements.[33] Although pentavalent bismuth compounds prefer their more electronegative ligands in apical positions, the hydroxyl groups in a glycol cannot both be in the apical positions for steric reasons. Therefore, chelation is most likely apical-equatorial as shown in structure 25.



25

The transition state from this intermediate to the products should involve steric or electronic interactions which favor phenylation of secondary hydroxyl groups over tertiary and axial hydroxyl groups over equatorial.

Conclusion

Use is already being made of pentavalent bismuth compounds in natural product synthesis both in the oxidation of allylic alcohols and in oxidative cleavage.[34] The oxidants are mild, nonelectrophilic and highly selective, and their use should continue to increase as a result of these properties.[2] The use of pentavalent bismuth compounds for carbon and oxygen phenylation should find broad application in organic synthesis. The specific phenylation of diols may prove to be very useful, and the ability of bismuth(V) compounds to oxidize functional groups other than alcohols and glycols should be studied further. Much more work must be done to understand clearly the mechanistic paths of the oxidations. The isolation or detection of intermediate 3 and its analogues should be a priority in such studies.

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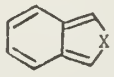
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ANNELATION OF TERTIARY BENZAMIDES VIA ISOBENZOFURAN AS THE INTERMEDIATE

Reported by Chin-Wen Chen November 21, 1983

Isobenzofuran (1) is a derivative of o-quinodimethane that reacts with typical dienophiles rapidly to give Diels-Alder adducts.[1] Although the system has been known for some time, the chemistry of isobenzofuran has not been studied extensively because the parent compound and its derivatives are difficult to prepare and it is more reactive in $[\pi^4s + \pi^2s]$ cycloaddition than its isoelectronic isomers, isobenzothiophene (2) and isoindole (3). The large scale preparation of isobenzofuran reported by Wierum



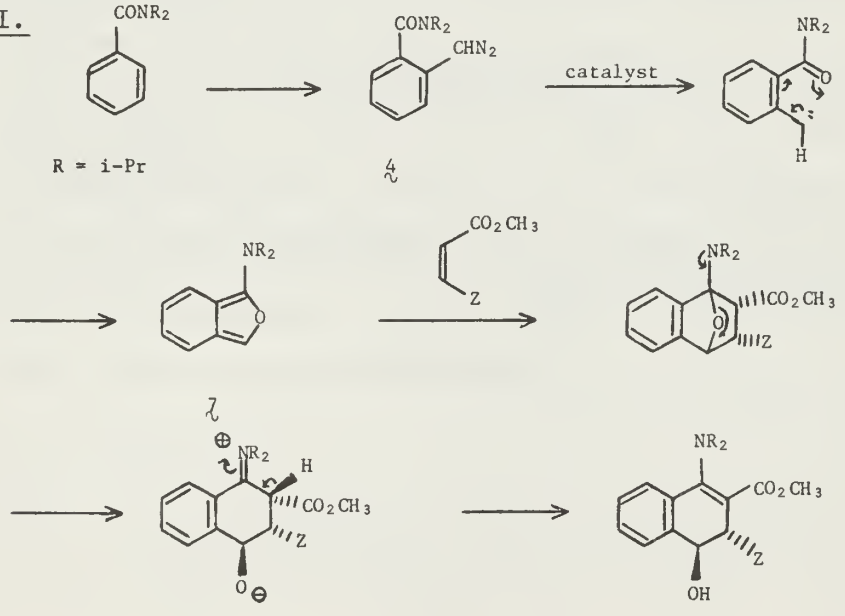
1 X =O
2 X = S
3 X = NH

utilizes flash-vacuum thermolysis of 1,4-epoxy-1,2,3,4-tetrahydronaphthalene.[2] Milder methods reported include thermolysis of 2-(α-bromoalkyl)benzophenone,[3] decomposition of o-acylphenyldiazomethane in the presence of catalytic amounts of a transition metal complex,[4] and hydrolysis of 1.3-dihydro-1,1-dimethoxyisobenzofuran with a trace of acetic acid.[5]

The regiospecific ortho-deprotonation of an aromatic hydrogen by base is of significant synthetic value.[6] Snieckus has made good use of this methodology for the preparation of a wide variety of natural products.[7] We are able to present an efficient synthesis of substituted 1-aminoisobenzofurans by using ortho-lithiation and electrophilic substitution as the initial steps. Further elaboration of the 1-aminoisobenzofuran with activated dienophiles proceeds rapidly and allows construction of a new ring with regio- and stereospecificity.[8]

The o-(α-diazomethyl)benzamide (4) can be synthesized via ortho-lithiation of N,N-diisopropylbenzamide followed by formylation, addition of hydrazine, and oxidation by nickel peroxide in 70% yield. Decomposition of the diazo compound 4 in the presence of a catalytic amount of a transition metal complex, e.g. $Cu(acac)_2$, and excess of a dienophile, such as methyl acrylate, gives the annelated products 5 as shown in Scheme I.

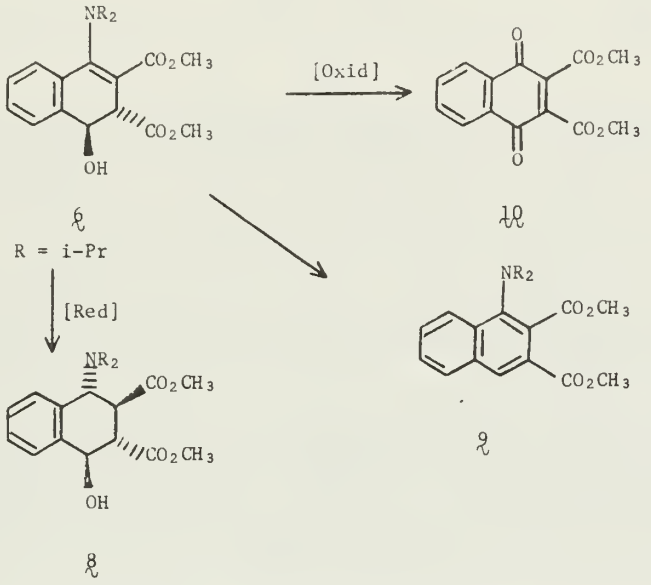
Scheme I.



5 Z = H
6 Z = CO_2CH_3

Presumably, the catalyst decomposes the diazo compound to generate a carbene center, which undergoes cyclization with the carbonyl group of the amide and forms a 1-aminoisobenzofuran 7. The cycloaddition of 7 and the dienophile takes place by a concerted endo addition with regio- and stereochemistry consistent with FMO theory. Evidence for this pathway is the formation of diastereoisomeric products in the addition to dimethyl maleate and dimethyl fumarate. The compound 6 can be further transformed into the substituted benzoquinone 10 by Collins oxidation and silver (II) oxide and can be reduced stereoselectively to the substituted tetrahydronaphthalene 8 by $Zn/CH_3OH/HOAc$. Also, it can be aromatized readily to 9 in the presence of acid or base as shown in Scheme II. Overall, the method leads to annelation

Scheme II.



of an aromatic ring with the possibility of introducing a nitrogen at the 1-position, an electron-withdrawing group at the 2-position, and a hydroxyl group at the 4-position with predictable regio- and stereochemistry. The 1-aminoisobenzofuran that serves as the versatile, common intermediate is derived from the readily available N,N-diisopropylbenzamide. Variations in the amide precursor and in the dienophile can lead to a myriad of products, all sustaining substitution patterns that would be difficult to achieve by other means.

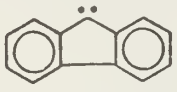
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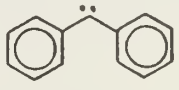
BORAANTHRYLIDENE: A PROBE OF STRUCTURE AND REACTIVITY FOR AROMATIC CARBENES

Reported by Stephen Lapin December 1, 1983

The chemical and physical properties of carbenes have been studied intensely over the past forty years. Many of these studies have centered around attempts to assign a particular chemical property to either the singlet or triplet spin state.[1] Two structurally similar carbenes with quite different properties are fluorenylidene (Fl) and diphenylmethylene (DPM).[1,2] These carbenes are conveniently generated by the photolysis of



Fl



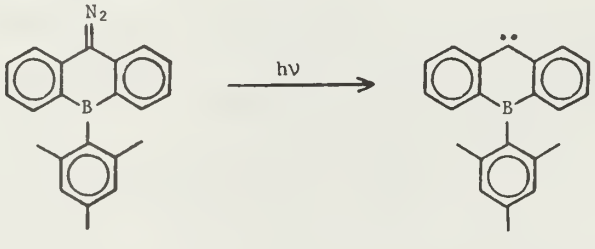
DPM

the corresponding diazo compound. Both Fl and DPM have been shown to be ground state triplets,[3] however, the magnitude of the energy gap between the singlet and the triplet (ΔG_{ST}) is different for the two carbenes. In the case of Fl the energy gap has been estimated to be less than 1.9 Kcal/mol.[4] Rapid equilibration between the two spin states allows Fl to undergo reactions associated with the singlet spin state if the appropiate trap is used. It reacts by direct insertion into a wide variety of olefins to give cyclopropanes in high yield, and it reacts nearly quantitatively with alcohols to give 9-fluorenyl ethers.[1,4]

As a consequence of a large energy gap (ΔG_{ST} = 4.6 Kcal/mol), DPM more commonly undergoes reactions associated with the triplet state.[1,5] It will react with terminal olefins by way of a diradical intermediate to give cyclopropanes. The reaction of DPM with alcohols results in hydrogen abstraction by the triplet to give the expected radical products in addition to the ether.[6]

There are two factors which could potentially explain the lower singlet-triplet gap for Fl compared to DPM. One explanation would be delocalization of the carbene electrons in the π system of Fl. This should lower the energy of the singlet. Delocalization would be less important in DPM since it is not a conjugated system. Another factor affecting ΔG_{ST} could be the bond angle at the carbene carbon. Theory predicts that the smaller bond angle of Fl would raise the energy of the triplet relative to the singlet.[7]

In an effort to determine how structure affects the properties of arylcarbenes, we have conducted an extensive analysis of 9-mesityl-9,10-dihydro-9-boraanthrylidene (BA), generated by the photolysis of 10-diazo-9-mesityl-9,10-dihydro-9-boraanthracene (DABA).

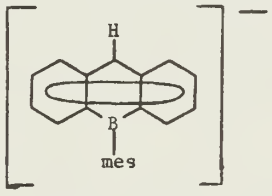


DABA BA

Introduction of the boron atom that converts Fl to BA provides a test of the influence of both the carbene carbon bond angle and the energy level of the π electron system on the magnitude of the singlet-triplet gap. Direct

irradiation of DABA leads first to the singlet carbene which undergoes intersystem crossing to the triplet with a rate constant of ca. $6.7 \times 10^9 s^{-1}$. Photosensitization with triplet 2-acetonaphthone gives the triplet carbene directly. The singlet carbene reacts with isopropyl alcohol to give the corresponding ether. The triplet carbene forms cyclopropanes non-stereospecifically from terminal olefins and abstracts hydrogen atoms from hydrocarbons and alcohols. Kinetic and product analysis shows that, in contrast to fluorenylidene, the rate of equilibration between ^{1}BA and ^{3}BA is slow compared with most of the bimolecular reactions of the triplet. This is believed to be a consequence of the larger energy gap between ground state ^{3}BA and ^{1}BA compared with that of Fl. We have estimated ΔG_{ST} to be greater than 5.0 Kcal/mol. for BA.

The boraanthracene anion (BAH^-) has been shown to be aromatic.[8] Meas-



BAH^-

urement of the pKa indicates that inclusion of the boron atom lowers the energy 8 Kcal/mol more than the fluorenyl anion. Thus, if stabilization of the singlet by delocalization in the π system were the critical factor, then the energy gap of BA should be smaller than Fl. This is opposite to the experimental results. We must therefore conclude that the bond angle is the major factor that determines the singlet-triplet energy gap.

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P-P π BONDING IN CARBON-ALUMINUM, CARBON-SILICON, AND CARBON-PHOSPHORUS COMPOUNDS

Reported by Charles F. Palmer, Jr. December 5, 1983

The formation of p-p π bonds is an accepted and well understood property of the second row elements carbon, nitrogen, and oxygen. In contrast to these elements, their third-row congeners are much less likely to form stable molecules involving p-p π bonding. It has been assumed that molecules with π bonds between elements of the second and third row were unstable and existed at best as short-lived intermediates. Many theoretical studies have been undertaken to understand the π-bonding between second and third row elements, but until recently synthetic routes to stable carbon-silicon and carbon-phosphorus compounds had not been developed. Only sulfur, tellurium, and arsenic had been known to form stable p-p π bonds until the last decade.

To explain why nearly all the p-p π bonds formed by third row and subsequent elements are unstable or nonexistent, arguments either referred to the large size of the atoms reducing the parallel overlap of the p orbitals or the diffuse nature or higher energy of np(n>2) p orbitals. Pitzer was the first to consider theoretically multiple bonding between elements of the third and lower periods. He held that the repulsion between the bonding p_x orbital of one atom and the filled inner shell of the other atom (inner-shell repulsion) explained the low π bond strength.[1] Mulliken calculated the overlap integrals for 2s-2s, $2p_\sigma$-$2p_\sigma$, $2p_\pi$-$2p_\pi$ and 3s-3s, $3p_\sigma$-$3p_\sigma$, $3p_\pi$-$3p_\pi$ bonds and found that the repulsion postulated by Pitzer would not be larger for third row elements compared to elements of the second row.[2] In fact, he found that the overlap integral values calculated for multiply bonded silicon were greater than those for carbon. He concluded that "the difference between second and third-row atoms with respect to readiness of formation of multiple bonds... is shown to be attributable to strengths of σ bonds in the third row."[2] This would indicate the polymeric form to be more stable than the monomeric double-bonded form. To account for this conclusion, many researchers have investigated the contribution of d-orbitals in bonding. No definitive proof concerning d-orbital contribution has been presented, because there have been many conflicting opinions about predictions based on their incorporation.[3] It seems impossible to conclude that d-orbital participation causes the general reluctance of the third row elements to form multiple bonds, although it is a factor to be considered in some cases.

Table 1

Approximate bond energies in kcal/mole[4]

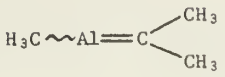
C—C	83	N—N	38	C—Si	73
C=C	146	N=N	100	C—P	63
C≡C	200	N≡N	226	C—Al	61
Si—Si	54	P—P	50		
Si=C	88	P≡P	125		

An examination of the recent advances in the study of carbon-aluminum, carbon-silicon, and carbon-phosphorus compounds sheds much light on the problem of the apparent instability of p-p π bonding in these compounds.

Carbon-Aluminum π Bonding

No compound with a carbon-aluminum multiple bond has yet been prepared in the laboratory. However, this is thought not to be due to the instability of the bonding in such molecules such as  or its inability to exist as an

isolated species, but due to its extreme reactivity.[5] The bonding in these



1

molecules was studied to predict properties of organoaluminum complexes and specifically the ability of aluminum to form multiple bonds to carbon.

Multiple bonds are predicted by Schaefer for certain electronic states of $AlCH_2$ and AlCH.[16] For $AlCH_2$, two doubly-bonded electronic states are predicted, $^2A_1$ and $^2B_2$, both with Al-C bond distances less than the 1.95 Å normally associated with an Al-C single bond. However, the ground state configuration for $AlCH_2$ has $^2B_1$ symmetry. Similarly for AlCH, one electronic state ($^1\Sigma^+$) appears to have a triple bond and represents a good confirmation of qualitative MO theory, but it is not the ground state configuration ($^3\Sigma^-$). Both ground states have a single Al-C bond. Whether multiple bonding in Al-C compounds will be observed in the future remains in question. It seems probable that the aluminum compound would be an anion salt.

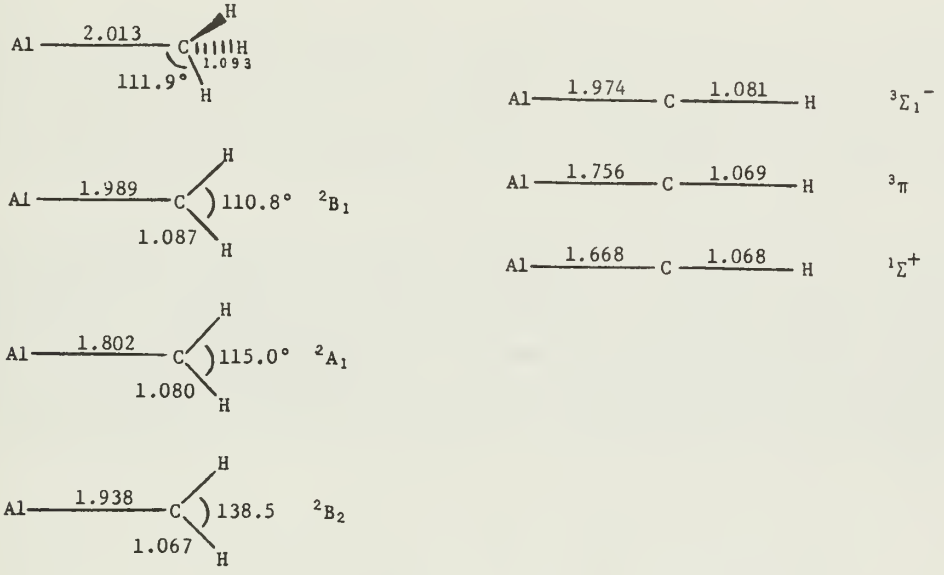


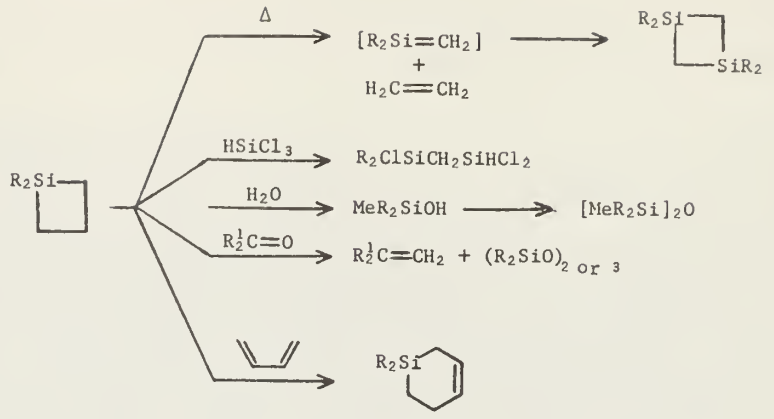
Figure 1. Predicted equilibrium geometries of several electronic states of AlCH, $AlCH_2$, and $AlCH_3$. Bond distances are in Å.

Carbon-Silicon π Bonding

The preparation of silicon analogues of organic multiply bonded compounds has been pursued for many years with little success until the last two decades. Ashe had much success with his preparation of carbon-phosphorus, carbon-arsenic, carbon-antimony, and carbon-bismuth double bonds in resonance stabilized pyridine analogues,[7] but all attempts to obtain similar silicon compounds failed.

The first evidence of silicon-carbon double-bonded species came in the thermolysis reactions of monosilacyclobutanes. These reactions have been extensively studied in the last fifteen years. A survey of their reactions is given in Scheme I. A silaalkene is an intermediate in all the above reactions. Its existence has been documented by mass spectrometry of the silaalkene in the gas phase,[8] as well as by IR spectroscopic studies.[9]

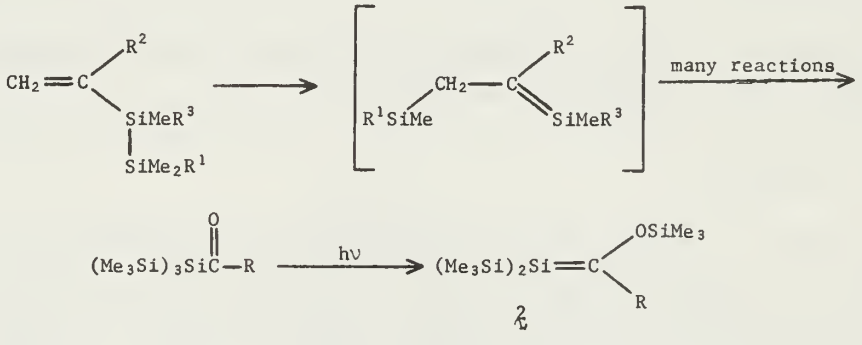
Scheme I



In addition to many addition reactions and cyclodimerization, the silaalkene intermediates generated participate in [2+2] and [4+2]cycloaddition reactions. The [2+2] cycloaddition reaction of silaethylenes proceeds more readily with compounds containing isolated C=O, C=S, or C=N double bonds. Silaethylenes also have proved to be good dienophiles in Diels-Alder-type reactions.

Sigmatropic rearrangements have also produced carbon-silicon double-bonded species. In one type of reaction, alkenyldisilanes are photoisomerized by the 1,3-migration of the silyl group, resulting in an intermediate that has many properties similar to those of simpler silicon-carbon double-bonded intermediates.[10] In another sequence, Brook and co-workers showed that acylpolysilanes on photolysis and thermolysis rearrange into silaethylenes (Scheme II).[11] This method has produced the first stable sila-

Scheme II



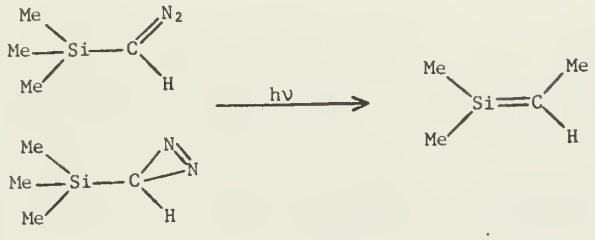
(a) R = CMe_3; (b) R = CEt_3; (c) R = 1-adamantyl

alkene 2c. This silaalkene has been isolated and characterized by IR, Raman, UV, ^{1}H NMR, ^{13}C NMR, ^{29}Si NMR, and mass spectroscopy and by its ionization potential. The X-ray crystal structure shows a slightly twisted molecule with a silicon-carbon double-bond length of 1.764 Å, significantly shorter than the normal length of a silicon-carbon single bond (1.87-1.91 Å).

Chapman and co-workers found that the irradiation of either (trimethylsilyl)diazomethane or (trimethylsilyl)diazirane matrix isolated in argon at

8K produces 1,1,2-trimethylsilaethylene.[12] The identity of the silaethylene was substantiated by the thermal dimerization at temperatures above 45K to give the corresponding disilacyclobutane (Scheme III).

Scheme III



It seems clear that there is no intrinsic instability in silaalkenes, but simply a thermodynamically-based propensity toward dimerization. The enhanced stability of silaethylene 2c can be attributed in part to steric factors which may inhibit its dimerization. The large substituents prevent the close approach of the molecules to each other. Electronic factors are also important. It has been calculated by Curtis that π bond overlap in silaethylene is smaller than in C_2H_4 and Si_2H_4 and that electron distribution is asymmetric, being localized primarily in the p orbital of the carbon atom. It has also been calculated that a simple carbon-silicon double bond would be significantly electropositive at silicon and electronegative at carbon.[13] Therefore simple silaalkenes, expected to be polarized like Z (Figure 2), readily undergo head-to-tail dimerization, but 2 fails in all cases to dimerize in this manner, even when non-bulky groups like methyl or trifluoromethyl are attached to carbon.[11] This probably results from the lack of strong polarization of the double bond because the electronic effects of the substituents oppose and largely neutralize the polarization arising from electronegativity differences.[11] ^{13}C NMR studies indicate that the sp2 carbon atom is strongly deshielded consistent with the acquisition of a positive charge from structures X and Y.[11]

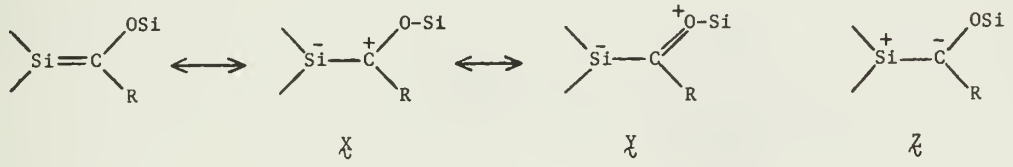


Figure 2.

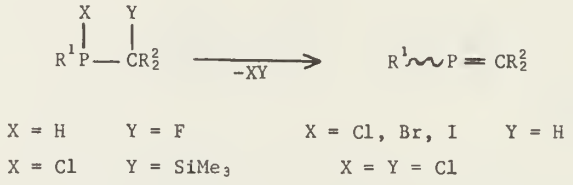
Theoretical studies of silaacetylene and its silylidene and vinylidene isomers by Schaefer et al. have laid the groundwork for the study of silicon-carbon triple bonds.[14] From calculations Schaefer predicts that the silylidene isomer is the lowest lying energetically and therefore the most likely to be observed experimentally. Silaacetylene itself would have a trans-bent equilibrium geometry, corresponding to a silicon-carbon bond order of approximately 2.5.

Carbon-Phosphorus p-p π Double Bonds

Research over the last seven years has seen many important advances in the preparation of stable double-bonded carbon-phosphorus compounds. In fact, the stability of the p-p π bond must now be accepted as fact.

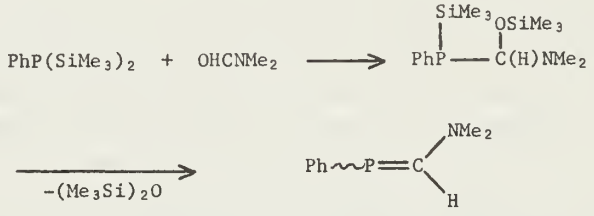
There are three basic synthetic routes to phosphaalkenes. The first, 1,2-elimination, has its driving force in the loss of two substituents of opposite polarity which combine in a thermodynamically favored leaving molecule (Scheme IV).[15] In general, it is possible to choose either a thermal or a base induced elimination.

Scheme IV



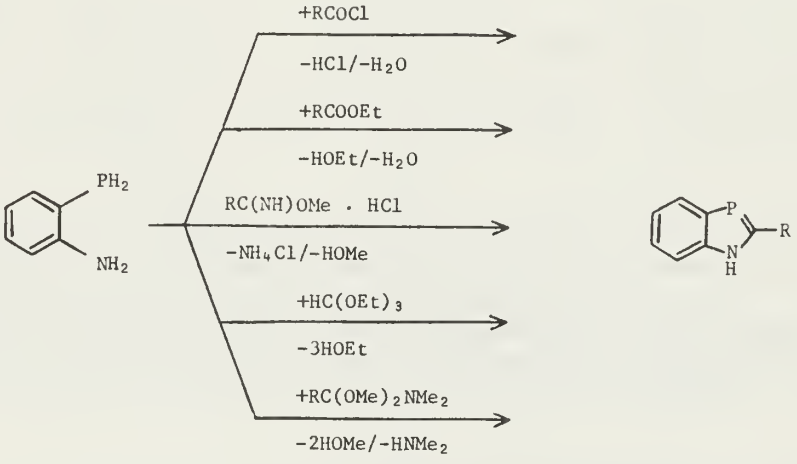
The second route is through a condensation step prior to a 1,2-elimination. The P-C bond may be formed by addition of a silylphosphane or a phosphane having a P-H bond to a carbonyl group, followed by an elimination step (Scheme V).[16] The formation of a P-C double bond is especially favored if

Scheme V



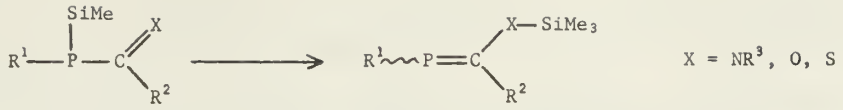
it is incorporated into a stabilizing ring skeleton. Accordingly, the condensation of o-phosphinoaniline with carboxylic acid derivatives such as esters, chlorides, amidoesters, orthoformic acid esters, or aminals leads to 1,3-benzaphospholes (Scheme VI).[17]

Scheme VI



The third method for the generation of the P-C double bond is based on the migration of a P-silyl group to an element such as nitrogen, oxygen, or sulfur that is in the α-position.[18] The double bond to the heteroatom is shifted to the phosphorus. The driving force of this rearrangement could be the formation of a very stable N-Si-, O-Si-, or S-Si bond (Scheme VII).

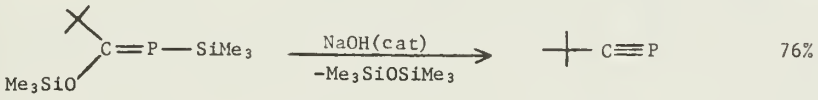
Scheme VII



Hundreds of double-bonded phosphorus-carbon compounds have been synthesized using these mehtods, and most are quite stable at normal temperatures. The compounds are mainly oily, often yellow colored substances. They are readily soluble in the usual polar or non-polar solvents. ^{31}P and ^{13}C NMR spectroscopy has been employed to characterize the compounds. Both the P- and C- nuclei of the P-C double bond show characteristic sp^2 downfield shifts. X-ray crystallographic studies also verify the geometries of these molecules.

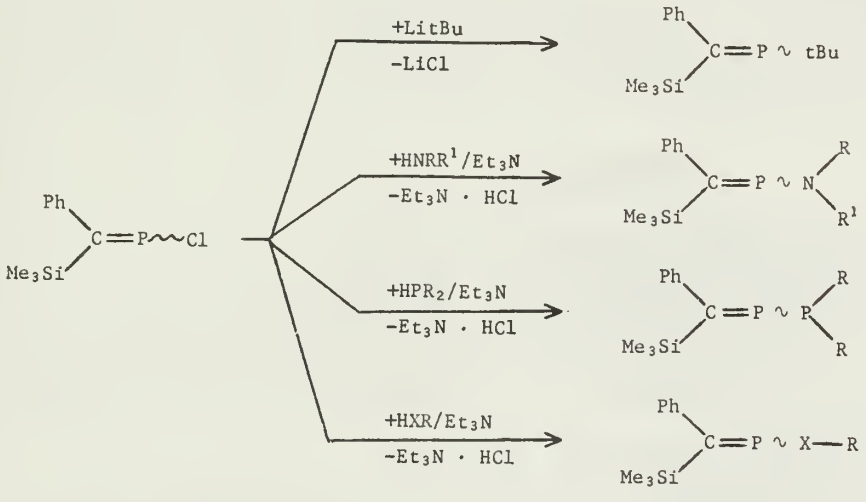
Becker and co-workers have reported the first synthesis of a stable phosphaalkyne in good yield (Scheme VIII). In this reaction hexamethyldisiloxane is eliminated from a phosphaalkene to give the corresponding phosphaalkyne.[19]

Scheme VIII



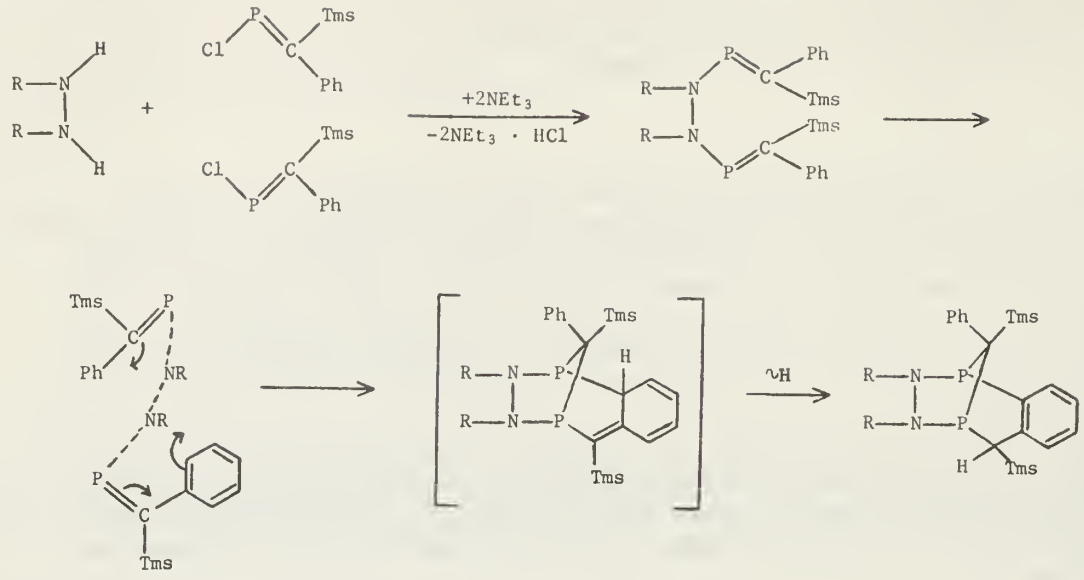
The reactions of phosphaalkenes have been studied extensively in recent years. Phosphaalkenes can undergo addition reactions of polar protic reagents as well as dimerization. These addition reactions are directed so that the anionic part of the HX molecule always adds to the phosphorus atom, while the proton adds to the carbon atom. Derivatizations at the phosphorus and carbon atoms with various substituent groups in molecules have been reported as shown in Scheme IX.[20] Phosphaalkenes also readily participate in pericyclic reactions. Appel has confirmed a Cope rearrangement in which a

Scheme IX



C-C bond and two P-P double bonds have been cleaved in favor of a P-P single bond and two olefinic double bonds.[21] He also reported a Diels-Alder-type reaction of a diphosphabutadiene analogue (Scheme X)[22] and the first synthesis of a diphosphabutadiene, though no details of those reactions were given.[23]

Scheme X



R = CH_3, Et, nPr, nBu, iBu

The reason that phosphaalkenes are more stable than silaalkenes, and these less so than carbon-sulfur double-bonded species, probably has to do with the electronegativity difference between the π-bonding atoms. As has been shown, in the absence of other electronic factors, π-electron density is much more heavily localized on the carbon atom than on the third row atom depending on the electronegativity difference. In sulfur compounds, this difference is not large and so the double bond formed is not heavily polarized, thus making the compound less reactive. The polarization increases in carbon-phosphorus, carbon-silicon, and carbon-aluminum compounds, making them increasingly reactive. Thus even though the compounds may have stable p-p π bonds, they may be too reactive to be isolated.

Conclusion

A stable silaethylene has now been synthesized, with more likely to follow. Many phosphaalkenes have been obtained, and the broad range of their synthetic uses is just beginning to be explored. These are some of the first in what will probably become a long list of carbon compounds previously thought unobtainable.

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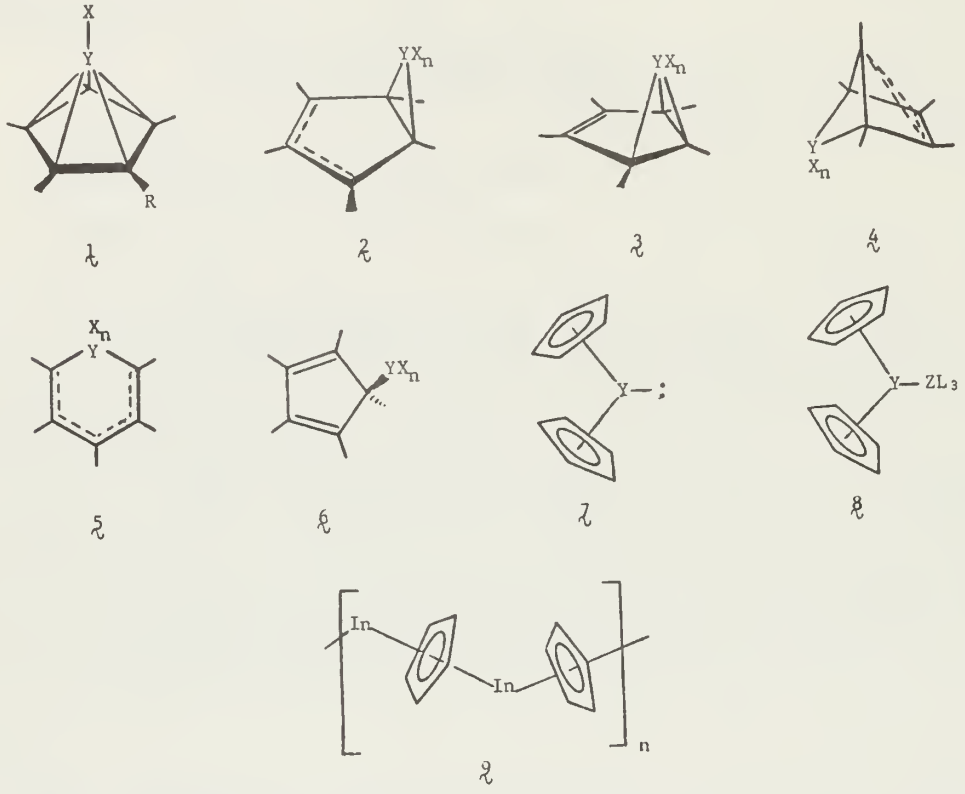
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MULTIHAPTO CYCLOPENTADIENYL COMPLEXES OF THE MAIN GROUP ELEMENTS

Reported by Paul Cahill December 12, 1983

Multihapto cyclopentadienyl - main group element complexes are common in the chemical literature but are less well known than their transition metal analogues. A wide range of reactivity, stability, and structure is observed, and many compounds of uncertain structure have been synthesized. This review is an attempt to systematize the known compounds into four isoelectronic families.



1 2 3 4 5 6 7 8 9

Electron-counting rules developed originally for boron hydrides[1] have been applied to transition metal clusters, main group clusters, and some organic compounds.[2] Molecules with six skeletal atoms (vertices) and eight skeletal electron pairs are predicted to exhibit nido cluster geometry as in 1. Representative molecules of this class are listed in Table I. Five

Table I

Representative nido clusters $(1)^+$

heteroatom (Y)	X	charge	R	ref.
Be	CH_3,Cl,Br, η^1-C_5H_5,I,BH_4	0	H	3
Mg	Br,Cl	0	H	4
B	Cl,Br,I, η^1-C_5Me_5	+1	$(CH_3)_5$	5
In	lone pair	0	H	6
Tl	lone pair	0	H	7
C	CH_3	+2	$(CH_3)_5$	8
Ge	lone pair	+1	$(CH_3)_5$	9
Sn	lone pair	+1	H,$(CH_3)_5$	10

+Predominantly ionic structures (e.g., Y = Li,Na,K) are omitted. Compounds with Y from groups V, VI, VII are unknown, as are compounds with Y = Al,Ga,Si,Pb.

of the eight electron pairs form the σ system of the C_5R_5 ring; the other three pairs fill the remaining skeletal molecular orbitals. The resulting "three-dimensional aromaticity" is used to rationalize the thermal stability of these compounds.[11]

Addition of one electron pair to a nido cluster generates an arachno cluster; structures 2-6 are related by this rule. Representative molecules adopting these structures are listed in Table II. The diversity of known

Table II

Representative arachno clusters (2-6)‡

YX_n	structure	hapticity	charge	ref.
Sn-pyr	2	η^2	+1	12
Sn-Cl	*		0	13
Al-(Cl)(CH_3)	3	η^3	0	14
C-(H)(CH_3)	2	η^2	+1	15
	4	--	+1	
	5	--	+1	
B-$(Cl)_2$	6	η^1	0	16

‡Molecules of uncertain structure include $(Me_5C_5)GeCl$,[9b] $(C_5H_5)TlMe_2$,[17] $[(Me_5C_5)PNMe_2]^+$,[18] $[(Me_5C_5)AsNMe_2]^+$.[18]

*Solid state structure shows distortion due to close intermolecular contacts.

clusters indicates that several local minima exist on the six vertex, nine electron pair hypersurface and that in some cases barriers between the local minima are sufficiently high to permit observation of more than one isomer for one YX_n.

Formal addition of one electron pair to 1 in the case where X = η^1-C_5R_5 does not give the expected arachno cluster. Instead, rearrangement occurs to give molecules with structure 7 for In,[19] Ge,[9a,20] Sn,[9a,20] Pb,[20] As[18,21] and Sb.[21] Lewis acid adducts (8) are also known.[21a,21b] These compounds contain fourteen interstitial electrons. The carbons in C_5R_5 ring are not symmetrically bonded to the central atom, and the electronic structure of 7 has only recently been calculated accurately.[20d,22]

One-dimensional chains (9) have been observed for CpIn, CpTl, and Cp_2Pb[20a,20b,23] (Cp_2Sn and $(Me_5C_5)_2Pb$ are monomeric in the solid state).[20e] No detailed study of the bonding in these solids has been reported.

The unique reactivity of several of these compounds has led to synthetic applications, especially with In and Tl.[24] Because of their high solubility in non-polar solvents, Cp_nY compounds are useful sources of Sn^{II}, Pb^{II}, In^{I}, etc.

The first example of C-H bond activation by a cyclopentadienyl non-metal cluster has been reported.[25] If the success of transition metal cluster chemistry can be used as a guide, rich chemistry from these non-metal clusters can be expected.

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ORGANIC SEMINAR ABSTRACTS

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SEMINAR TOPICS

Spring Semester, 1984

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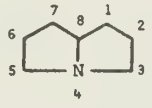
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THE PYRROLIZIDINE ALKALOIDS - RECENT SYNTHETIC APPROACHES

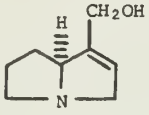
Reported by George Mahler January 30, 1984

Diverse in their distribution in nature and potent in their biological activity, the pyrrolizidine alkaloids have been extensively examined[1] and continue to be a center of study for chemists and biochemists alike. The disease pyrrolizidine alkaloidosis affects most species of domestic livestock, is often enzootic in distribution, and has been known by many different names in different countries.[2] The foundations of chemical knowledge of these alkaloids were laid in the period 1930 to 1950, mainly in the laboratories of Men'shikov in Moscow and Roger Adams of Illinois, through whose efforts the structures of the amino-alcohols heliotridine and retronecine were elucidated (Chart I). This seminar concerns recent approaches

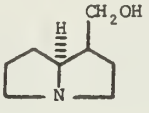
Chart I



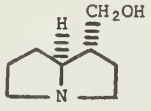
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Pyrrolizidine



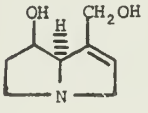
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Supinidine



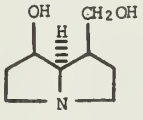
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Isoretronecanol



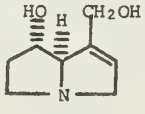
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Trachelanthamidine



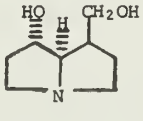
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Retronecine



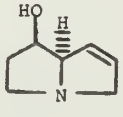
6
Platynecine



7
Heliotridine



8
Dihydroxyheliotridane



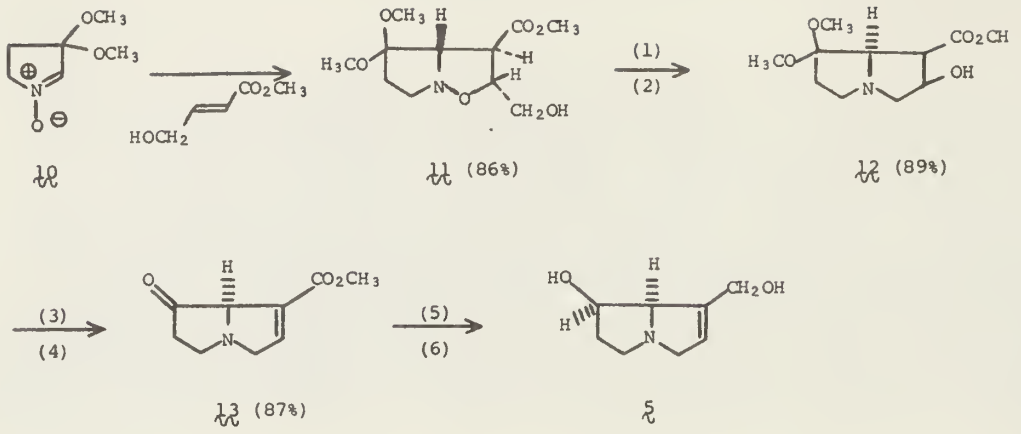
9
Turneforcidine

to the synthesis of the pyrrolizidine nucleus as well as recent developments in the asymmetric synthesis of several pyrrolizidine alkaloids.

Synthesis via 1,3-dipolar cycloadditions

In 1980, Tufariello[3] reported a highly stereo and regioselective synthesis of (±)-retronecine, 5. Paralleling a previous synthesis of the alkaloid cocaine[4], functionalized nitrones[5] were used in the key regiospecific carbon-carbon bond forming step (Scheme I).[6]

Scheme I

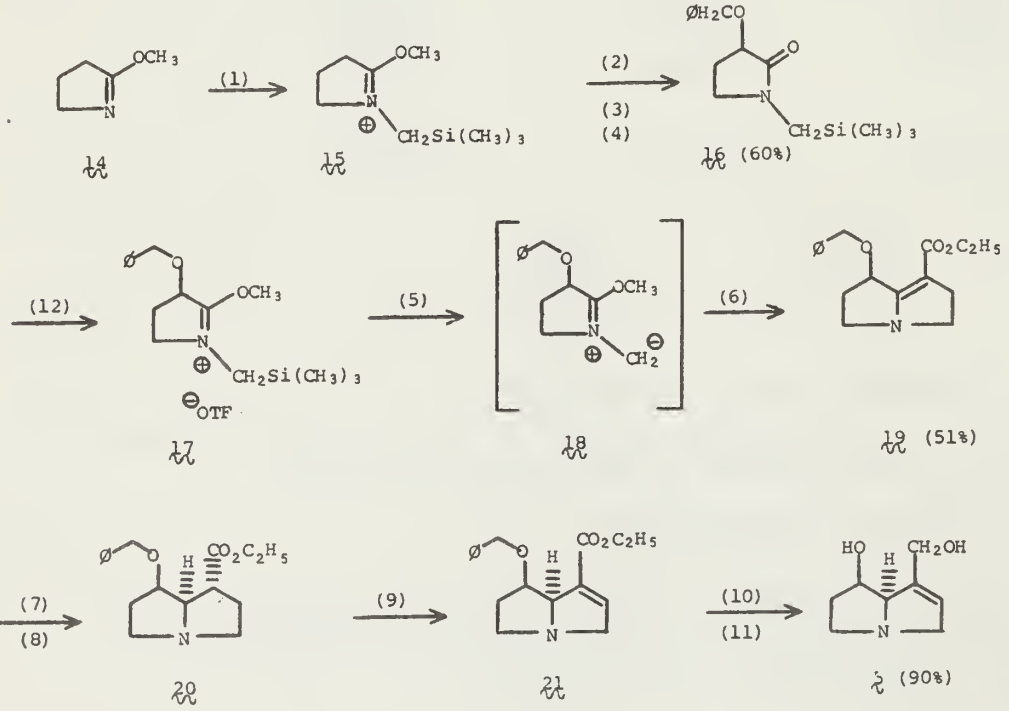


(1) $MeSO_2Cl$, Et_3N, CH_2Cl_2 (2) H_2, Pd/C, CH_3OH (3) $MeSO_2Cl$, Et_3N, CH_2Cl_2
(4) 37% HCl (5) $NaBH_4$ (6) AlH_3

Condensation of the ketal nitrone 10 with methyl γ-hydroxycrotonate lead stereospecifically to isoxazolidine 11 uncontaminated with other possible regio- and stereoisomers. Reduction of the mesylate of the isoxazolidine occurred with simultaneous nucleophilic displacement of the mesylate to yield the substituted pyrrolizidine 12.

In 1979, Vedejs reported the first synthetically viable route to non-stabilized iminium ylides[7] as well as their 1,3-dipolar cycloadditions to give pyrrolines.[8] This methodology was extended in 1980 to the synthesis of (±)-retronicine, 5, (Scheme III).[9,10]

Scheme III

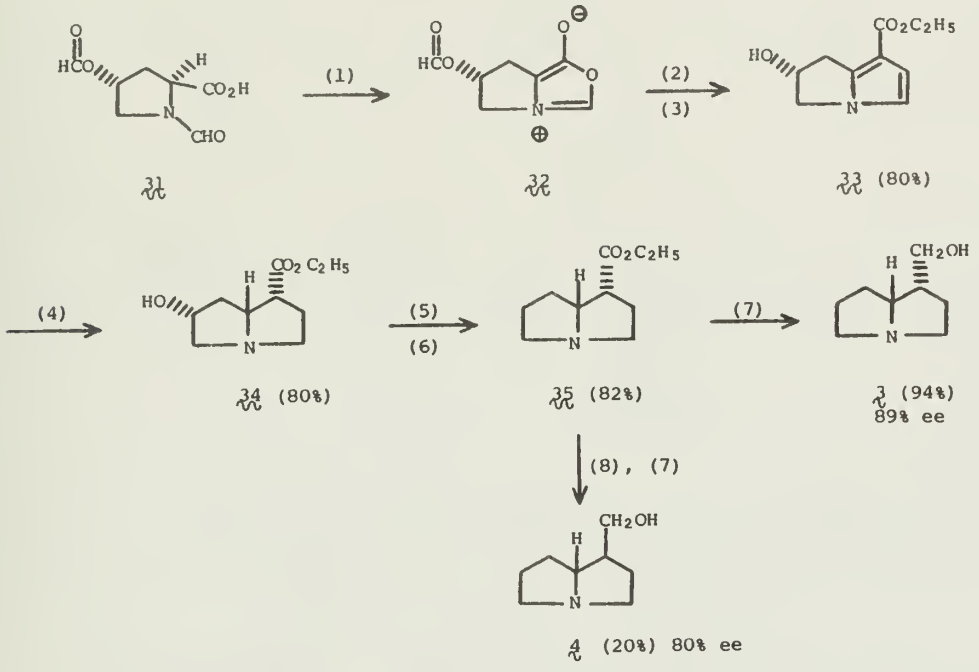


(1) $CF_3SO_2CH_2Si(CH_3)_3$ (2) 1,4-Diazobicyclo[2.2.2]octane (3) LDA, $Mo_2O_5 \cdot Py \cdot HMPA$ (4) NaH, $PhCH_2Br$ (5) CsF (6) $HC{\equiv}C-CO_2C_6H_5$ (7) H_2, Pd/C (8) R.T. ~ 12 hrs. (9) LDA, ϕ_2Se_2, MCPBA (10) DiBAL-H (11) 3eq. Li/NH_3 (12) $CH_3SO_3CF_3$

Treatment of the salt 26 with cesium fluoride followed by trapping with ethyl acrylate yielded the cycloadduct 28 (51% yield based on lactam 25), which was presumed to be formed by a 1,3-dipolar cycloaddition of imidate methylide 27 generated in situ. No indication was given as to why hydroxylation of the lactam to yield 25 occurs preferentially on the β face of the molecule. Though as yet unapplied to this class of compounds, more recent work[11] has involved using thiolactams as azomethine ylide precursors because of their ease of alkylation and greater stability.

The synthesis of optically active pyrrolizidine bases has also been achieved by 1,3-dipolar cycloadditions. Robins[12] in 1981 reported the synthesis of (+)-isoretronecanol, 3, and (+)-trachelanthamidine, 4, of greater than 80% optical purity starting from the N,O-diformyl derivative of readily available (-)-4-hydroxy-L-proline (Scheme IV).

Scheme IV



(1) Ac_2O (2) $HC\equiv C-CO_2C_2H_5$ (3) NH_3, EtOH (4) H_2, Pd/C (5) Cl_2 (6) H_2 (7) $LiAlH_4$ (8) $NaOC_2H_5$, EtOH

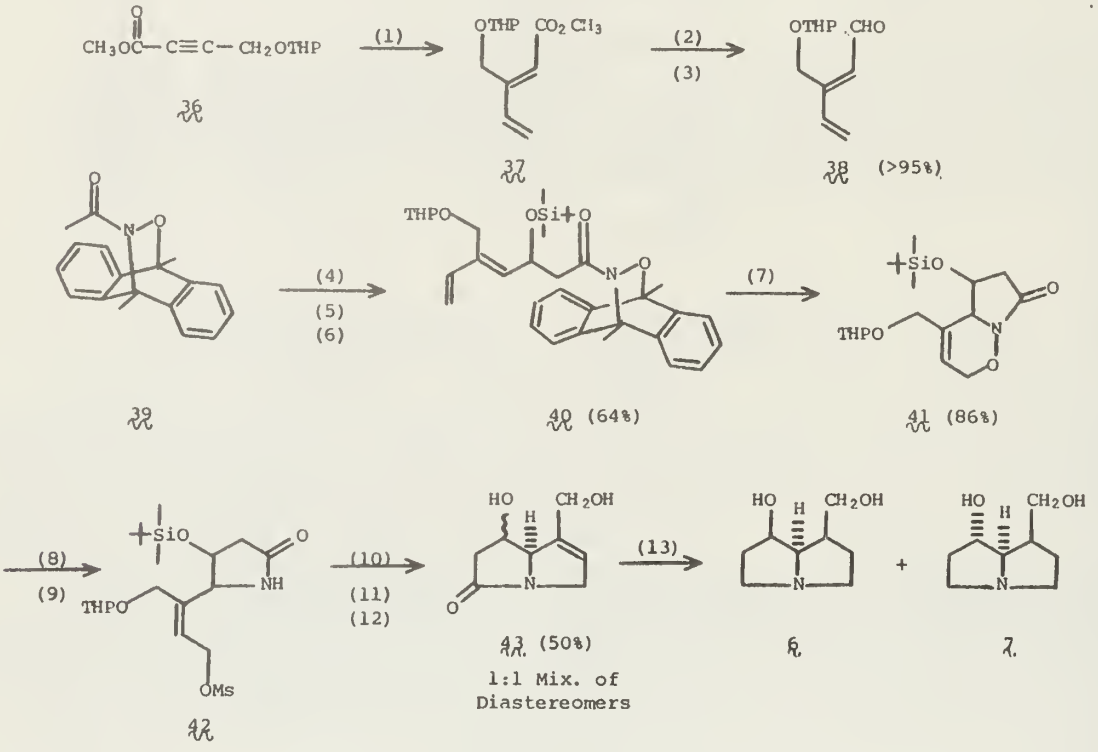
Known to be a reactive 1,3-dipole, the 1,3-oxazolium-5-olate, 32, also known as a "münchnone,"[13] was prepared by cyclodehydration of the N,O-diformyl amino acid. Condensation with ethyl propiolate with simultaneous loss of carbon dioxide, followed by catalytic hydrogenation, gave the hydroxy ester 34 as the only product, delivery of hydrogen being from the less hindered β face of the molecule. Epimerization of the ester 35 to the thermodynamically more stable exo form allowed for synthesis of the diastereomeric (+)-trachelanthamidine, 4, in 20% yield of 80% optical purity. The synthesis of (-)-isoretronecanol and (-)-trachelanthamidine was similarly accomplished after inversion of configuration of C_6 of ester 33 by S_N2 displacement of hydroxide with the formate anion.

Synthesis by 4+2 cycloaddition

The technique of intramolecular dienophile transfer, developed by Keck[14] in 1978, was extended in 1980 to the synthesis of (±)-heliotridine, 7, and (±)-retronecine, 5, (Scheme V).[15]

Diels-Alder adduct 39 was obtained by trapping the acyl nitroso dienophile with 9,10-dimethylanthracene. Thus, slow addition of acetoxyhydroxamic acid to a solution of 9,10-dimethylanthracene and tri-n-propylammonium periodate afforded 39 in 80% yield. Thermolysis in benzene under reflux produced the 1,2-oxazine 41 as a 1:1 mixture of diastereomers, implying little stereoselectivity in the Diels-Alder addition.

Scheme V



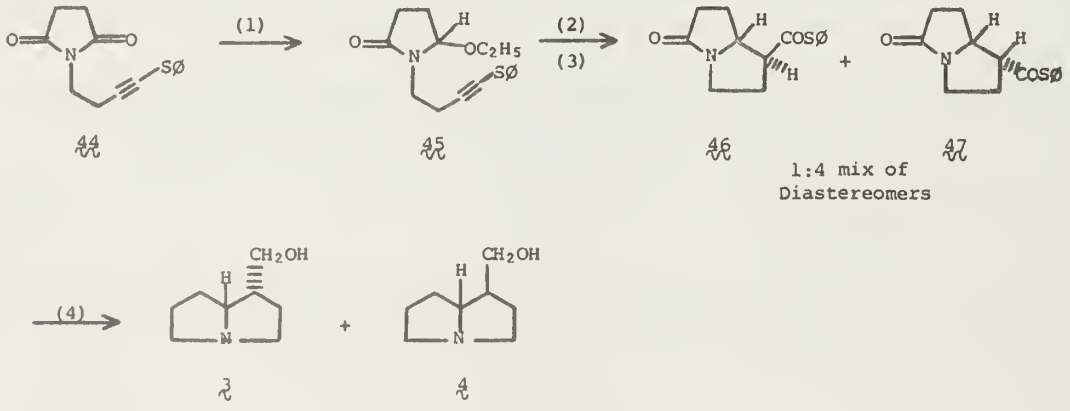
(1) $LiCu(C_2H_3)_2$ (2) DiBAL-H (3) MnO_2 (4) LDA (5) 38 (6) $(CH_3)_3CSi(CH_3)_2Cl$
(7) ø-H, Δ (8) $LiAlH_4$ (9) MsCl, Et_3N (10) LDA, 23°C (11) H^+ (12) $F^\ominus$ (13)·$LiAlH_4$

Synthesis involving acyliminium ions

The focus of considerable work in recent years,[16] acyliminium ions and cycloadditions thereof have been used with success in the synthesis of the pyrrolizidine nucleus.

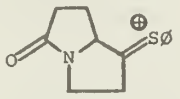
In 1979, Speckamp [17] reported the site-specific ring closure of the phenylthioacetylene imide 44 to yield (±)-trachelanthamidine, 4, and (±)-isoretronecanol, 3, (Scheme VI). That the only products observed

Scheme VI

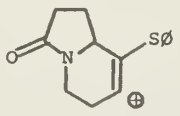


(1) $NaBH_4$, EtOH (2) HCOOH (3) 2M HCl (4) $LiAlH_4$

resulted from 5-exo-dig ring closure could be rationalized in terms of increased stability of the intermediate linear vinylogous cation, 48 over 49. The increased stereoselectivity in acyliminium ion cyclizations as reflected in the final product distribution is also to be noted.



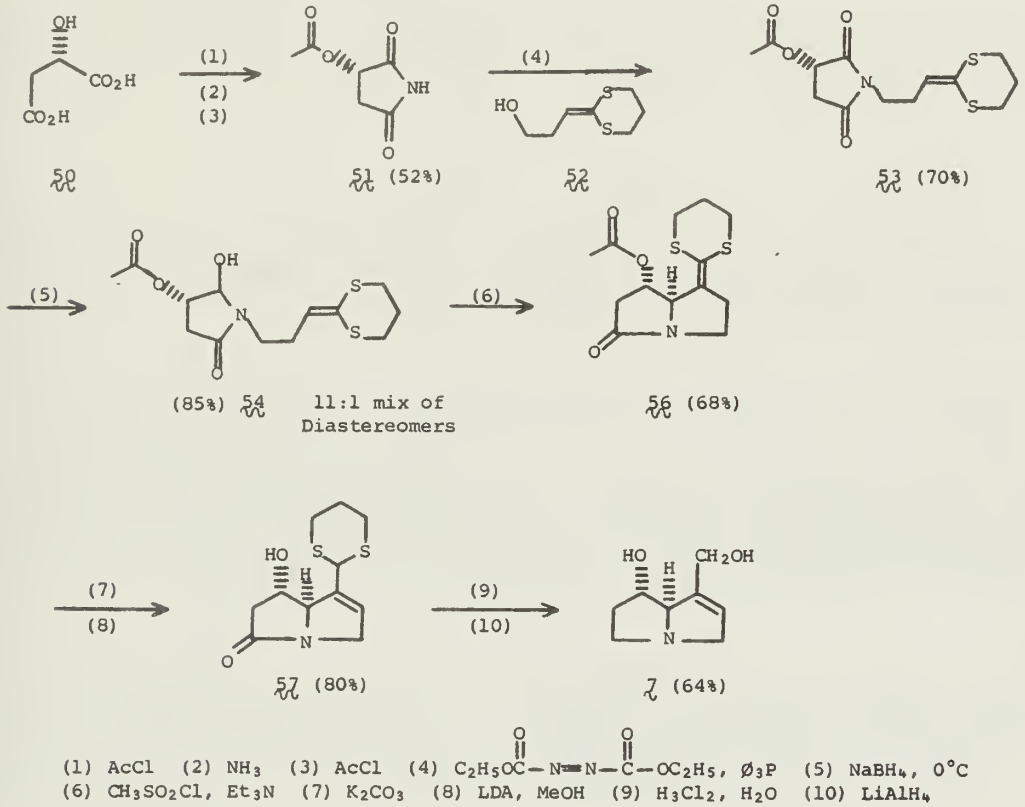
48



49

Optically enriched pyrrolizidines have been synthesized by analogous methodology developed by Chamberlin[18,19] using the ketene thioacetal group as a cationic cyclization terminator (Scheme VII). As well as yielding the

Scheme VII



50 51 (52%) 52 53 (70%)

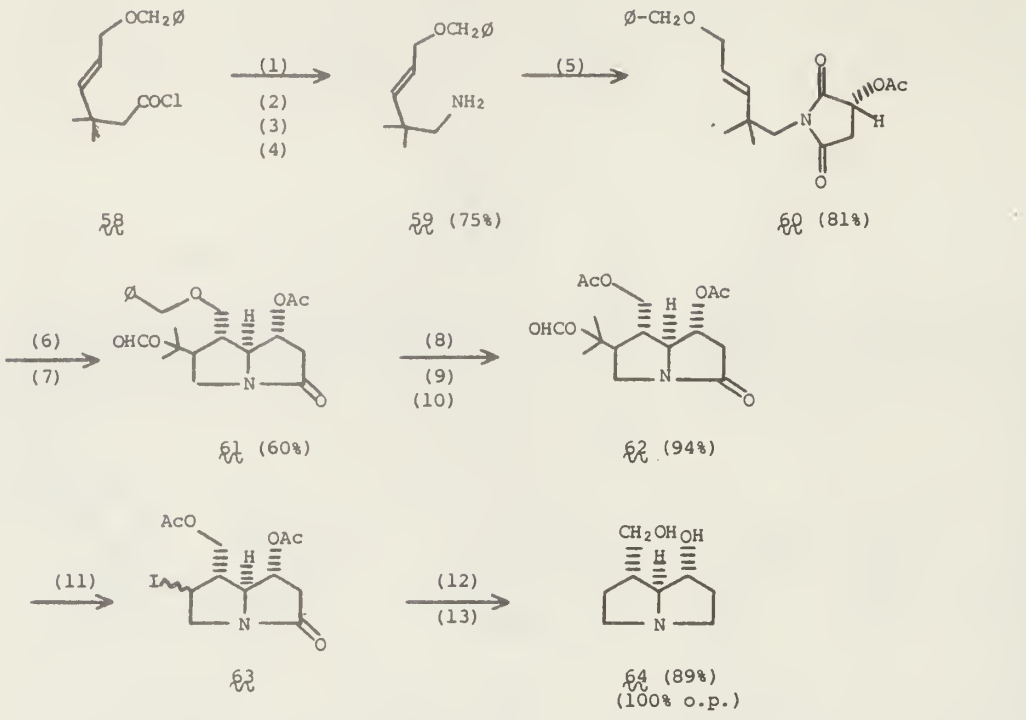
(85%) 54 11:1 mix of Diastereomers 56 (68%)

57 (80%) 7 (64%)

correct stereochemistry of the product, the acetoxy group effectively blocks the α face of the lactam 54 from attack-forcing the condensation to proceed exclusively as indicated. The migration of the double bond (56 → 57) was accomplished by taking advantage of the propensity of lithiated ketene thioacetals to protonate α to sulfur.[20] Optically pure (+)-heliotridine, 7, was obtained upon hydrolysis and reduction of dithiane 57. Ketene thioacetal alcohol 52 was prepared in one step by reaction of γ-butyiolactone with bis-(dimethylaluminium)-1,3-propanethiolate.[21]

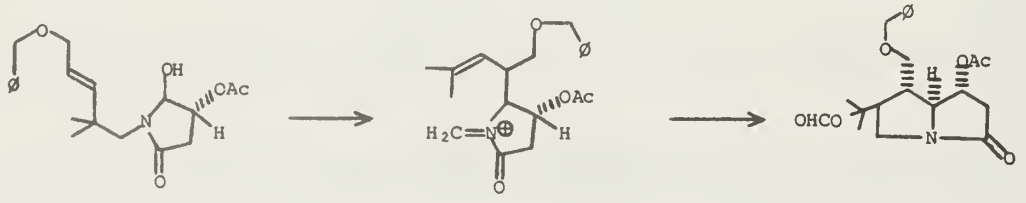
Paralleling the work done by Chamberlin, Hart[22] in 1982 reported the synthesis of trachelanthamidine, 4, and supinidine, 2, and in 1983 reported the enantioselective sythesis of (-)-hastanecine[23] through the agency of N-acyl-2-aza-1,5-hexadiene rearrangements (Scheme VIII). Condensation of amine

Scheme VIII



(1) NaN_3 (2) Ø-H, Δ (3) $KOBu^+$ (4) CF_3CO_2H (5) R-Acetoxysuccinic Anhydride (6) $NaBH_4$ (7) HCO_2H (8) NaOH, CH_3OH (9) H_2, Pd (10) Ac_2O (11) HgO, I_2 (12) $(n\text{-}Bu)_3SnH$ (13) $LiAlH_4$

59 with R-acetoxysuccinic anhydride proceeded without racemization to yield the chiral imide 60, which cyclized specifically on the β face to yield lactam 61. Oxidative degradation of the side chain at C-5 proceeded with difficulty in the presence of the benzyl ether, but cleanly if the primary and secondary hydroxyls were acetylated. The rearrangement-cyclization is believed to involve an initial N-acyl-2-aza Cope rearrangement to afford the N-acyl iminium ion 66 followed by cyclization to the lactam 61.

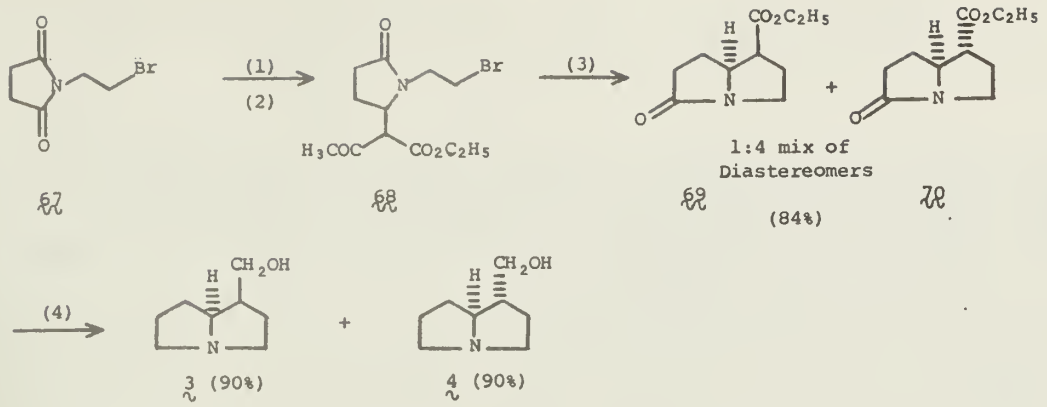


65 66 61

Miscellaneous synthetic methods

In recent years, several disparate syntheses of pyrrolizidine alkaloids have appeared in the literature. In 1980, Kraus[24] reported what he described as the "most direct and operationally convenient synthesis of isoretronecanol, 3, and trachelanthamidine, 4," by an amide alkylation[25] reaction sequence (Scheme IX). Under conditions allowing kinetic control of ring closure, i.e. sodium hydride followed by sodium cyanide in dimethylformamide, a 1:1 mixture of diastereomeric amides 69 and 70 was formed. As an attempt to generalize the methodology and allow for entry into more complex pyrrolizidine alkaloids both β-ketosulfones and β-carboethoxysulfones were tested as active methylene compounds. Unfortunately, neither class of compound gave any amido alkylation product, presumably due to the low enol content of such compounds.

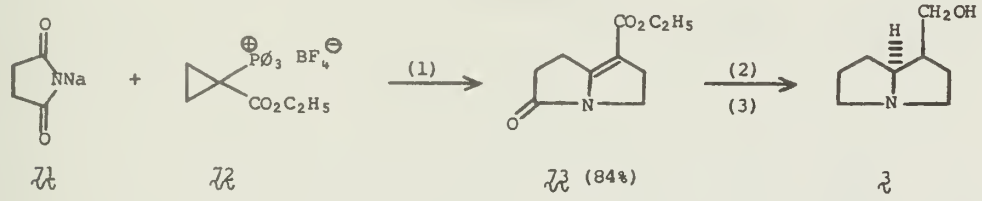
Scheme IX



(1) $NaBH_4$, EtOH (2) $CH_3COCH_2CO_2C_2H_5$, $AlCl_3$ (3) $NaOC_2H_5$, EtOH (4) $LiAlH_4$

The use of 1-carboethoxycyclopropyltriphenylphosphonium tetrafluoroborate[26] as a potent electrophile and phosphorus ylide equivalent was exploited by Flitsch[27,28,29] in the synthesis of racemic isoretronecanol, 3, (Scheme X).

Scheme X

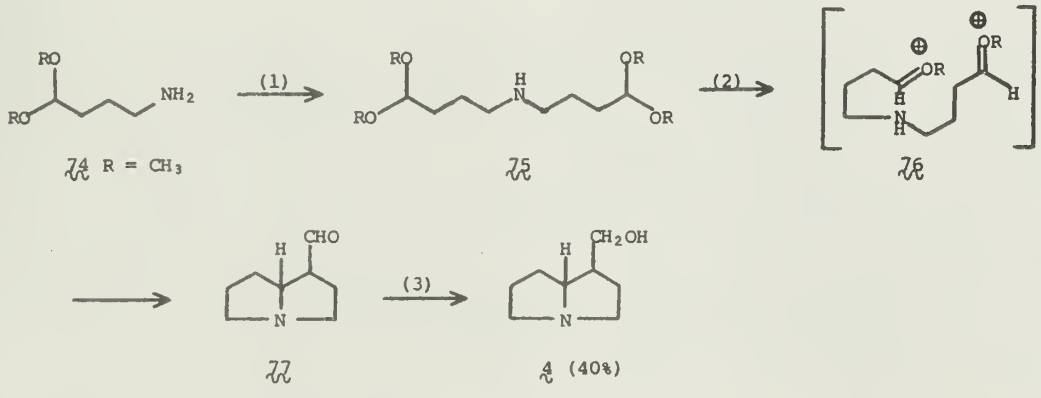


(1) xylene, Δ (2) H_2, Pt (3) $LiAlH_4$

Reaction of the cyclopropylphosphonium salt with the anions of glutarimide and diformyl imide resulted in the production of the analogous indolyidine and pyrrolidine in high yield. That the amido ester obtained after hydrogenation could be epimerized to the thermodynamically more stable exo form allowed for the synthesis of racemic trachelanthamidine, 3, in comparable yield.

Several biomimetic syntheses of racemic and optically pure trachelanthamidine have been reported.[30,31,32] Naturally occurring trachelanthamidine is believed to arise from a Mannich reaction of the symmetrical amino aldehyde 76, (Scheme XI, R=H) formed by decarboxylative deamination and

Scheme XI

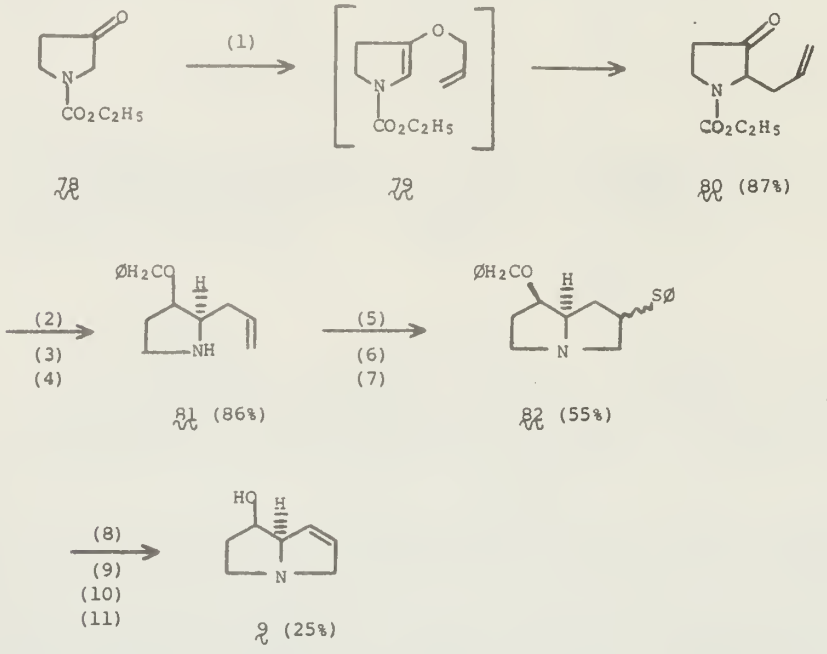


(1) W-2 RaNi (2) Δ, MeOH, HCl (3) $NaBH_4$

coupling of two ornithine units. Though the deaminative dimerization with Raney nickel has been reported,[39] difficulty was encountered with trimerization. By using pyridinium (+)-camphor-10-sulfonate in aqueous medium for the cyclization, (+)-trachelanthamidine, 4, of 33% optical purity could be obtained.

The total synthesis of racemic turneforcidine, 9, has been accomplished using the unique and recently developed cyclization of ω-unsaturated alkenylamines using phenylsulfenyl chloride, termed sulfenocyclamination (Scheme XII).[34] Presumably proceeding through an epi-sulfonium ion,[35] the

Scheme XII



(1) $HOCH_2CH{=}CH_2$, (+)-Camphor-10-Sulfonic Acid (2) $NaBH_4$, MeOH
(3) Ø-CH_2-Br, NaH, DMF (4) KOH, Diglyme (5) HCl, MeOH (6) Ø-S-Cl
(7) K_2CO_3, NaI (8) HCl (9) MCPBA (10) Heat (11) $PdCl_2$, HCl.

ring closure proceeds primarily to yield the endo product with no exo product observed. Though this is readily appreciated due to the strain involved in forming a four-memebered ring, such site selectivity has also been observed in the synthesis of pyrrolidines and piperidines, uncontaminated with isomers arising from endo ring closure.

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INTRINSIC STABLE ISOTOPE SHIFTS IN ^{13}C NMR

Reported by Paul A. Keifer February 2, 1984

It is well known that the replacement of a given nucleus in a molecule with another isotope can alter the chemical shifts of other nuclei in the molecule. The differences in chemical shifts between the two isotopomers are called isotope shifts. The observed isotope shifts for any given molecule are either equilibrium isotope shifts, in which the isotope alters the position of a dynamic equilibrium process and, hence, the average chemical shifts, or intrinsic isotope shifts, in which the isotope directly alters the nuclear shielding of the observed nucleus. While equilibrium isotope shifts in ^{13}C NMR are usually large and downfield (5-50 ppm), intrinsic isotope shifts are typically much smaller (<1 ppm) and upfield (Table 1). Secondary isotope shifts are those which occur for an observed nucleus which is of a different element than the element undergoing isotopic replacement (e.g., isotope sifts seen in ^{13}C NMR spectra when ^{1}H is replace with ^{2}H), whereas primary isotope shifts occur for an observed nucleus of the same element as that undergoing isotopic replacement (e.g., isotope shifts seen in ^{13}C NMR spectra when ^{12}C is replaced with ^{13}C). Both primary and secondary intrinsic isotope shifts are useful not only in assigning NMR resonances, but in solving a variety of mechanistic, kinetic, and biosynthetic problems.

Table 1. Typical Ranges of Intrinsic Isotope Shifts Observed in ^{13}C NMR Spectra

Original Nucleus (δ_1)	Isotope Nucleus (δ_2)	Isotope Shift of Observed ^{13}C Nucleus in ppm ($\delta_2-\delta_1$).[a,b]
$^{13}C-^{1}H$	$^{13}C-^{2}H$	α = -0.2 to -1.2, β = -0.04 to -0.2, γ = -0.02 to -0.08
$^{13}C-O-^{1}H$	$^{13}C-O-^{2}H$	-0.06 to -0.24
$^{13}C-N-^{1}H$	$^{13}C-N-^{2}H$	α = -0.06 to -0.40, β = -0.02 to -0.06
$^{13}C-^{12}C$	$^{13}C-^{13}C$	-0.002 to -0.012
$^{13}C-^{14}N$	$^{13}C-^{15}N$	-0.001 to -0.04
$^{13}C-^{16}O$	$^{13}C-^{18}O$	α = -0.01 to -0.05, β = -0.006 to -0.008
$^{13}C-^{35}Cl$	$^{13}C-^{37}Cl$	-0.004
$^{13}C-^{32}S$	$^{13}C-^{34}S$	-0.009

a. α = shift over one bond, β = shift over two bonds, γ = shift over three bonds...
b. negative values are upfield shifts

Theory

Theoretical treatments of the intrinsic isotope shift have focused on either the shortening of bond lengths or the decrease in vibrational amplitudes caused by heavy isotope substitution.[1,2] Either effect would draw the electrons closer to the nucleus bonded to the isotope, causing increased nuclear shielding and an upfield shift of its resonance and, to a lesser extent, deform the electronic distributions of nearby nuclei in a similar fashion, thereby causing their nuclear shieldings to also increase. Less popular explanations for the isotope shift include changes in solvation due to isotopic substitution or changes in magnetic shielding due to different populations of excited vibrational states. (Downfield ^{1}H NMR isotope shifts

seen for deuterated formaldehyde and ammonium ions may well be due to differences in solvation; a deuterium atom can hydrogen bond better than a proton due to a smaller vibrational amplitude, and hydrogen bonding causes downfield shifts in ^{1}H NMR spectra.[3])

Theoretical models based on rotational and vibrational kinetic energies have proven useful for understanding diatomic and small polyatomic molecules.[4] Jameson[5] used vibrationally and rotationally averaged nuclear shieldings to generate a theoretical model consistent with the generally observed trends of isotope shifts:[1] 1) substitution by a heavier isotope normally results in upfield shifts, 2) the isotope shift decreases with distance, 3) the larger the mass difference upon substitution, the larger the isotope shift, and 4) the magnitude of the shift is approximately proportional to the number of isotopic substituents.

Recent studies have proposed using a number of simultaneous phenomena to explain observed isotope shifts. Two groups have used hyperconjugation and the unequal populations of rotamers to explain isotope shifts in alkylbenzenes;[6,7] one group proposed using isotope shifts to probe systems for evidence of hyperconjugation. A recent study of naphthalenes and azulenes, however, presented long-range intrinsic isotope shifts which could not be fully explained by hyperconjugation, inductive effects, or simple vibrational factors. They concluded that none of the mechanisms described in the literature is sufficient to explain some of the long-range isotope effects.[8]

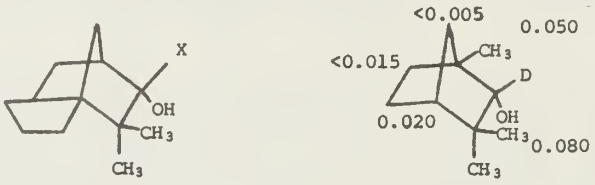
^{13}C-^{2}H Isotope Shifts

The most commonly used isotope shift is that observed by exchanging C-^{1}H for C-^{2}H. This results in a carbon triplet (1:1:1) due to the spin of deuterium and a decrease of the total intensity for the resonance of the directly bonded carbon; without deuterium decoupling, this can result in a near disappearance of the carbon's resonance. This problem has been addressed by Wesener and Gunther[9] and Doddrell, et al.,[10] who developed selective pulse techniques to discriminate between various degrees of deuterium substitution. These techniques allow for the separation and identification of CD, CD_2, CD_3, CHD, CHD_2, and CH_2D groups within a molecule.

A good example of the applicability of deuterium isotope shifts to signal assignments is a series of papers by Tulloch,[11] who selectively introduced deuterium at various sites in C_{18} aliphatic esters and derivatives and monitored the α,β, and γ isotope shifts on both sides of the deuterium-bound carbon. Bell, et al.,[12] found that substituents on isotopomeric benzene rings affect the isotope shifts; increased electron density at a given carbon atom was associated with an increase in the upfield isotope shift. McInnes, et al.,[13] in an interesting study, used deuterium isotope shifts to study the biogenetic pathway of n-heptadecane.

Isotope shifts caused by heavy atom substitution are characteristically upfield, but downfield shifts have been observed. Wehrli[14] and Jeremic[15] reported isotope shifts up to six bonds away in cyclodecanones, with some downfield isotope shifts seen in α-deuterio ketones. No explanation of the downfield shifts were given; however, Aydin and Gunther reported downfield intrinsic isotope shifts for distant carbons in monodeuterated cyclopentane and cycloheptane.[16]

The effects of deuterium substitution on neighboring carbons has been shown to be stereochemically dependent. Ernst used a monodeuterated vitamin B_{12} derivative to show that deuterium has a stereospecific effect on vicinal methyl groups.[17] The vicinal isotope shift varied with the dihedral angle; no isotope shift was seen with a 96° dihedral angle, but an isotope shift of -0.069 ppm was seen for the methyl group at a 24° angle. Jurlina and Stothers studied the dihedral angle correlation in greater depth.[18] Isotope shifts for a polycyclic alcohol pair (1a, 1b), as well as for endofenchol (Figure 1), were consistent with the theory that maximum isotope shifts occur when the dihedral angle is near 0° or 180°. From these data it is clear that caution must be used when isotope shifts from carbon-bound deuterium are used to assign ^{13}C NMR resonances.



1a X = H
1b X = D

Figure 1. Stereochemical Dependence of Vicinal Isotope Shifts.

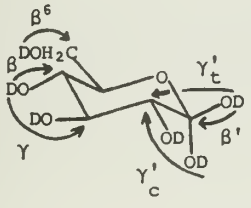
^{13}C-O-^{2}H and ^{13}C-N-^{2}H Isotope Shifts

While isotope shifts generated by carbon-bound deuterium have proven useful, the effort involved in the synthesis or biosynthesis of the labeled compounds inhibits wide use of the technique. A simpler method is to label the active hydrogens of a molecule. This is easily achieved for C-O-H and C-N-H protons by solution in deuterium oxide. The only requirement for observing resonances for isotopomers of this type is that the residence time of the isotope (^{1}H or ^{2}H) must be longer than the inverse of the isotope shift in hertz. To achieve reproducible results, however, detectable amounts of both isotopomers must be present in solution, since concentration effects can obscure isotope shifts found by comparing two different spectra. Two types of experiments have been designed which conform to these requirements.

In the first type of experiment, two portions of the sample are required. One portion contains normal hydrogen, while the other is partially deuterated by exchanging several times with deuterium oxide. Both halves are lyophilized and known quantities of each dissolved in a non-protic solvent. The spectrum is run as usual and inspected for isotopic doublets, which normally indicate HO- or HN-bearing carbons. One of the first reports of this technique was by Gagnaire and Vincendon, who studied carbohydrates dissolved in deuterated dimethyl sulfoxide.[19] An alternative technique was used by Newmark and coworkers,[20] who dissolved the compounds (alcohols and phenols) in the same solvent, ran the spectra, added equimolar amounts of deuterium oxide for each hydroxyl group present, and reran the spectra. Occasionally calcium sulfate was added to remove water and slow hydrogen exchange. The resulting mixture of isotopomers produced isotope shifts for most hydroxyl-bearing carbons, although phenols with electron withdrawing substituents produced no detectable isotope shifts, presumably due to increased exchange rates.

Reuben[21] and Christofides and Davies[22] were able to determine both the signs and magnitudes of all isotope effects from only one spectrum of a given carbohydrate. In this technique, the OH:OD ratio is adjusted by adding water to solutions of the deuterated compound in deuterated dimethyl sulfoxide. The exact extent of deuteration is determined by ^{1}H NMR spectroscopy, and the observed ratio used to calculate the intensity ratios of the signals within each series of multiplets; multiplets are observed for each ^{13}C resonance due to the number of possible isotopomers generated in polyhydroxy compounds, especially carbohydrates. This procedure also detected the presence and direction of intramolecular hydrogen bonding.

In the second type of deuterium exchange experiment, two isotopomerically pure solutions are separated in a coaxial tube which is designed to allow equal volumes of the two solutions to lie in any given cross section of the receiver coil. This technique, first proposed by Pfeffer and coworkers,[23] consists of placing a solution of the sample dissolved in water in the inner tube, and an equimolar solution of the sample dissolved in deuterium oxide in the outer tube. A routine spectrum allows appropriate upfield shifts to be observed for the sample in deuterium oxide. In Pfeffer's original paper, as well as later publications,[24] the technique was applied to carbohydrates, and a linear regression analysis of the isotope shift magnitudes for many compounds gave values for various contributions to the observed isotope shift, as illustrated in Figure 2. The coaxial tube technique was also used for the detection of vinyl alcohol formed <u>in situ</u> (and related stability determinations),[25] while a methanolic version of the technique was applied to two macrolide antibiotics bearing numerous hydroxyl groups.[26] In this case, the isotope shift clearly identified all carbinol carbons and their neighbors, and distinguished ester carbonyls from the free carboxylic acids.



β = -0.14, shift due to any hydroxyl group except anomeric or primary hydroxyl groups. Affects directly bonded carbon.

β' = -0.11, shift due to anomeric hydroxyl group.

β^6 = -0.15, shift due to primary hydroxyl group.

γ = -0.03, shift due to any hydroxyl group (except anomeric and primary). Affects carbons two bonds away.

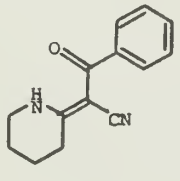
γ'_t = -0.06, shift due to anomeric hydroxyl group.

γ'_c = -0.03, shift due to anomeric hydroxyl group.

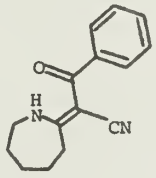
(all values in ppm, s.d. < 0.02 ppm)

Figure 2. Typical Contributions to the Observed Isotope Shifts in Carbohydrates.

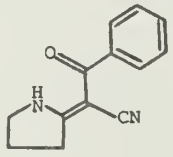
Tautomeric equilibria have also been studied by Pfeffer's coaxial tube technique. Coppola distinguished tautomers of enamino systems,[27] and demonstrated for the compounds shown below that tautomers are seen for the six- and seven-membered cyclic amines (1 and 2), but the double bond prefers to remain exo to the five-membered ring in compound 3. Similar studies on tautomeric equilibria has been carried out on β-thioketones by Hansen.[28]



1



2



3

Isotope shifts due to deuterium exchange have also been observed in amines and amides; this has been most useful in the spectral assignments of amino acids and peptides. Feeney, et al.,[29] in 1974, studied peptides in a water:deuterium oxide (1:1) solution and resolved doublets for the carbonyl carbons of amides. Carboxylate carbons and carbons bearing amino groups were singlets due to rapid exchange with the solvent. The rate of exchange of the amide hydrogens was regulated by pH and the isotope shifts were not observed at all pH values. Primary amides could be distinguished by the triplet (NH_2, NHD, ND_2) produced for the carbonyl carbon (spacing of 0.066 ppm), whereas peptide carbonyls appeared as doublets (NH, ND, with a spacing of 0.100 ppm).

Ladner and coworkers[30] studied a series of aliphatic amino acids and dipeptides, and observed isotope shifts for amine, amide, and carboxylic acid groups. They concluded that there is a simple correlation between the magnitude of the isotope shift, the number of deuterons directly bonded to nitrogen, and the distance between the exchange site and the observed carbon. Linear regression analysis produced average isotope shifts (per deuteron) of -0.093 ppm for nitrogen-bearing carbons, -0.033 ppm for carbons two bonds removed from a nitrogen atom, and -0.226 ppm for carboxylate carbons. Aromatic and aliphatic amides were studied by Newmark and Hill,[31] who obtained similar isotope shifts for the aliphatic systems. For carbons one bond from nitrogen a range of -0.08 to -0.10 ppm was found, while a range of -0.02 to -0.06 ppm was seen for carbons two bonds from nitrogen. The corresponding isotope shift ranges for aromatic amides were -0.08 to -0.011 ppm and -0.07 to -0.10 ppm. These values were obtained from samples dissolved in dimethyl sulfoxide to which equimolar amounts of water and deuterium oxide were added (typically 10% of the solvent volume).

A later study by Led and Peterson[32] demonstrated that isotope shifts observed for selected amino acids (glycine, lysine, and alanine) in deuterium oxide were due not only to intrinsic isotope shifts, but were also due to isotope effects on pKa values. Large chemical shift changes (up to 1 ppm) were possible when the pH of the observed solution was close to the pKa value of an amino acid.

^{13}C-^{13}C Isotope Shifts

Isotope shifts in ^{13}C NMR have also been produced by nuclei other than hydrogen. There are reports of isotope shifts due to isotopes of carbon, nitrogen, oxygen, chlorine and sulfur. The isotope shifts due to ^{13}C isotopes are the hardest to measure; in general, these measurements require labeled compounds, and the isotope shifts are calculated by determining the center frequency of the doublet due to ^{13}C-^{13}C coupling. Jokisaari[33] observed isotope shifts ranging from 0.012 ppm downfield to 0.027 ppm upfield for four-membered rings and heterocycles, with isotope shifts being seen over both one and two bonds. Booth and Everett[34] discovered a conformational dependence of the isotope shifts for cis-1,4-dimethylcyclohexane; however, all isotope shifts were upfield.

An occasional problem with the ^{13}C NMR spectral analysis of products partially labeled with ^{13}C is determining which resonances are singlets and which are multiplets due to ^{13}C-^{13}C coupling. This has been addressed by Nakashima and Rabenstein,[35] who used spin-echo NMR to distinguish resonances due to coupling from resonances of isolated ^{13}C nuclei. This

technique can be especially useful in biosynthetic studies using [^{13}C,^{18}O] acetate where, in the NMR spectrum of the product, a closely spaced doublet could be due to either an ^{18}O isotope effect on an isolated carbon, or due to long-range ^{13}C-^{13}C coupling; spin-echo techniques can make the assignment straightforward.

^{13}C-^{15}N Isotope Shifts

Isotope shifts due to ^{15}N have recently been detected. In 1980, Wasylishen[36] reported a ^{13}C NMR isotope shift of -0.0045 ppm for the C-1 carbon of aniline, and isotope shifts of -0.02 to -0.04 ppm for inorganic cyano complexes containing ^{15}N. He suggested that larger ^{15}N isotope shifts are correlated with larger C-N bond orders. Bremard, et al.,[37] reported values of -0.025 to -0.030 ppm for oxime complexes; in favorable cases a two-bond isotope shift could be seen. Studies on mixtures of ^{14}N and ^{15}N-labeled azobenzene and benzo[c]cinnoline were conducted by Kuroda and Fujiwara,[38] who found α-isotope shifts of -0.013 to -0.015 ppm and β-isotope shifts of -0.003 to -0.005 ppm.

Isotope shifts due to ^{15}N were shown to be useful in biosynthetic studies of proteins in a report by Kainosho and Tsuji.[39] They grew Streptomyces on media containing various ^{15}N-labeled amino acids. The use of different labeled amino acids produced proteins labeled at different positions. By knowing the amino acid sequence of a protein, and knowing which ^{13}C resonances belonged to which types of amino acids (by using ^{13}C-labeled amino acids), they were able to assign the carbonyl resonances of various methionine residues to their locations in the peptide chain. The methionine carbonyl carbons appeared as isotopically shifted doublets when the adjacent amino acids were ^{15}N labeled. The procedure should prove to be a general one, allowing precise ^{13}C resonance assignments to be made for any proteins of microbial origin. This should eventually enable studies of the structure and dynamics of a protein backbone to be made by ^{13}C NMR.

^{13}C-^{18}O Isotope Shifts

By far the most well studied of the isotope shifts produced by non-hydrogen nuclei has been the ^{18}O isotope shift. Oxygen-17 can be used, but it is more expensive due to its lower natural abundance (0.037%) and produces an isotope shift of smaller magnitude. The oxygen isotope shifts are useful in the study of biosynthetic pathways, especially with poly-oxygenated substances, where the alternative method of label location, mass spectrometry, usually requires either extensive degradation or site-specific labeling. Oxygen isotope shifts have also been used in resonance assignments and in studies of kinetic and mechanistic processes.

A significant contribution to the study of ^{18}O isotope shifts in ^{13}C NMR has been a series of papers by Risley and Van Etten.[40-46] These reports have covered the effects of substituents, bond order, and steric size, and have used the isotope shift to follow the exchange kinetics of t-butyl alcohol, acetic acid, and two carbohydrates, as well as to follow the hydrolysis rate of a substituted oxirane. The authors demonstrated that the isotope shifts were different for different classes of compounds, and indicated that they were additive (in multiply labeled orthocarbonates) and were independent of solvent.[41] The additivity of the isotope shifts was further verified by Vederas in studies of mono- and di-^{18}O labeled acetals.[47]

Vederas and coworkers also studied the structural dependence of the isotope shift.[48] Their results agreed with those of Risley and Van Etten, and both found that the ^{18}O isotope shift decreases over the range of 0.05 to 0.01 ppm upfield, in the order: ketones≥aldehydes≥esters≥amides≥ethers and alcohols. Wtih sp^2 bonded oxygens, conjugation decreases the magnitude of the isotope shift. They also found that, within a functional group, there is an approximate correlation between the carbon-oxygen bond length and the magnitude of the isotope shift. With ethers and alcohols, the isotope shift varies with the hybridization of the directly bound carbon atom. In alcohols, it was also shown that the magnitude of the isotope shift decreases in the order: tertiary alcohols≥secondary alcohols≥primary alcohols≥phenols. Vederas found a solvent dependence in the alcohol isotope shift.

A recent paper by Everett[49] stated that a close linear relationship exists between the magnitude of the one-bond isotope shift and the chemical shift of the carbon atom in carbonyl groups. Risley and Van Etten used a more limited set of the same data, and found no such correlation.[44]

In the last three years over 15 papers have been published on ^{18}O isotope shifts. This isotope shift has been used to study reaction pathways of triepoxide rearrangements.[50] mechanisms of mercapto alcohol chlorination,[51] and the mechanism of alkylation in sulfonic esters.[52] Studies of biosynthetic pathways, however, have been abundant. The first such report was a study of averufin, an aflatoxin B_1 precursor, by Vederas,[53] who demonstrated that out of seven oxygen atoms in each molecule, six came from [^{18}O] acetate and one came from $^{18}O_2$. The amount of oxygen exchange with the medium was also determined. Vederas and Hutchinson[54] also studied macrolide biosynthesis using [^{13}C, ^{18}O] propionate or butyrate to form lasalocid A. Cane and coworkers[55] have used [^{13}C,^{18}O] acetate and propionate to determine the source of various oxygen atoms in polyoxygenated macrolides such as the erythromycins, the avermectins, and monensin A.

As mentioned before, when using ^{13}C, ^{18}O labeled precursors in biosynthetic studies, closely spaced doublets are often observed. Distinguishing between long-range ^{13}C-^{13}C coupling or ^{18}O isotope shifts on any given ^{13}C atom can be difficult. This can be solved either by extensive dilution of the labeled precursor with unlabeled compound, or by using various pulse techniques to distinguish between the two types of resonances. A spin-echo pulse sequence was used by Nakashima and Vederas[56] to distinguish ^{13}C-^{13}C long-range coupling from isotope shifts in sterigmatocystin, another aflatoxin B_1 precursor. Out of six oxygens, four were found to be derived from acetate; this determination limited the possible rearrangement mechanisms proposed for the formation of sterigmatocystin.

^{13}C-^{37}Cl and ^{13}C-^{34}S Isotope Shifts

Isotope shifts due to ^{37}Cl and ^{34}S have also been observed in ^{13}C NMR. Isotope shifts for carbons directly bound to chlorine were about -0.004 ppm when measured for hexachloropropene, hexachlorobutadiene, and tetrachlorobutenyne.[57] The isotope shifts appeared to be additive, and the 3:1 isotope ratio of chlorine was well reflected in the multiplet intensities for mono-, di-, and tri-chlorinated carbons. Isotope shifts due to sulfur were considered to be the cause for an upfield resonance of ca. 10% intensity seen

in the ^{13}C NMR spectrum of non-enriched carbon disulfide, due to 4.2% ^{34}S natural abundance.[58] The isotope shift was -0.009 ± 0.001 ppm. While the sulfur isotope shift may find limited use in ^{13}C NMR, it is expected that the chlorine isotope shift might be found useful in studies of polychlorinated hydrocarbons.

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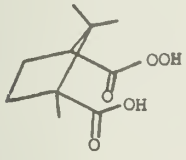
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ASYMMETRIC EPOXIDATIONS

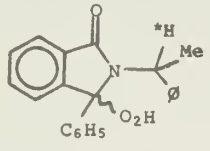
Reported by Daniel Reno February 6, 1984

The regio- and stereoselective methods available for the chemical conversion of the epoxide functional group make it one of the most useful functionalities in organic synthesis.[1] Asymmetric oxidation of olefins to produce optically active epoxides is, therefore, a very valuable synthetic transformation.

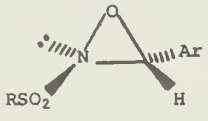
Asymmetric epoxidation has been achieved by the oxidation of olefins with chiral peracids, 1, and hydroperoxides, 2; however, the enantioselectivity obtained with these reagents has been low, <10% ee.[2-4] A low asymmetric bias occurs with these reagents because the chiral centers are several bonds removed from the reacting center; and the asymmetric center, therefore, has little influence on the transition state geometries.[5] The lack of complexation between these chiral reagents and olefins compounds the problem.



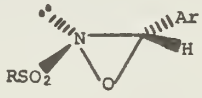
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2



3



4

R = 3-bromocamphor-9-yl Ar = 2-chloro-5-nitrophenyl

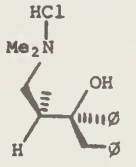
Davis, et al., have reported the use of optically active 2-sulfonyloxaziridines 3 and 4, prepared by m-chloropenbenzoic acid (m-CPBA) oxidation of the sulfonylimines and fractional recrystallization of the diastereomeric products, as enantioselective epoxidizing agents.[6] These reagents have produced optical enrichments of 12-40% ee for the oxidation of non-functionalized olefins. The sulfonyloxaziridines are more successful than the peracids and hydroperoxides because the asymmetric centers are adjacent to the reacting center, and the chiral centers, therefore, have a more pronounced effect on the energy difference between the diastereomeric transition states. The asymmetric induction is believed to be primarily controlled by the minimization of steric interactions in the transition state.

The abiltiy of cytochrome P 450 to catalyze various oxidations prompted Groves and coworkers to investigate iron porphyrins as epoxidation catalysts.[7] Asymmetric epoxidation was achieved with α,β,α,β-tetrakis (o-aminophenyl) porphyrins appended with two different sets of chiral ligands. The porphyrins appended, by means of amide linkages, with (R)-α-phenylpropionic acid and 1,1'-binaphthyl-2,2'-dicarboxylic acid gave enantioselective oxidations of 10-31% and 7-51% ee, respectively, for the styrene derivatives investigated. The degree of asymmetric induction was influenced considerably by changes in the steric environment of the olefin. A rationalization for the asymmetric induction has yet to be devised for the porphyrins.

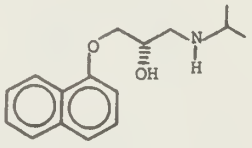
Transition metals, such as molybdenum, vanadium, and titanium, appended with chiral ligands have been used as catalysts for asymmetric epoxidations.[1,8-14] The most successful and extensively studied system is the titanium-tartrate catalyzed epoxidation of allylic alcohols.[1,10,11,13,14] This system produces enantiomeric enrichments of >90% ee. The titanium-tartrate catalyst has also been used in the kinetic resolution of racemic secondary allylic alcohols.[11]

The selectivity of the titanium-tartrate system has been attributed to several factors: (i) the allylic alcohol and t-butyl peroxide are coordinated to the metal; (ii) the coordinated distal peroxo-oxygen, the one not bonded to carbon, is transfered to the olefin; (iii) the proximal peroxo-oxygen interacts strongly with the titanium in the transition state, resulting in conformational restriction of the peroxo-oxygen; (iv) the olefin attacks the distal peroxo-oxygen by an S_N2-type approach; and (v) the π^* orbital of the olefin must overlap with one of the lone electron pairs of the oxygen being delivered.[13] The first four points are sufficient to explain the kinetic resolution of secondary allylic alcohols, but do not account for the enantioselectivity in the oxidation of the prochiral systems. The fifth point was hypothesized to account for the enantioselectivity.

Application of the titanium-tartrate system to synthetic problems has been quite successful.[14] It has been used for the enantioselective synthesis of propoxyphene, 5, (58% yield, >95% ee), propranolol, 6, (65% yield, >95% ee), and frontalin, 7, (74% yield, >95% ee). This catalytic system has found application in the kinetic resolution of secondary allylic alcohols used to synthesize endobrevicomin, exobrevicomin, and other compounds.



5



6



7

To summarize, the asymmetric epoxidation of olefins has proven quite successful for allylic alcohols, but more efficient methods need to be found for simple olefins.

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NEW SYNTHETIC APPROACHES TO POLYSUBSTITUTED PYRROLIDINES

Reported by Tom Sowin

February 9, 1984

Introduction

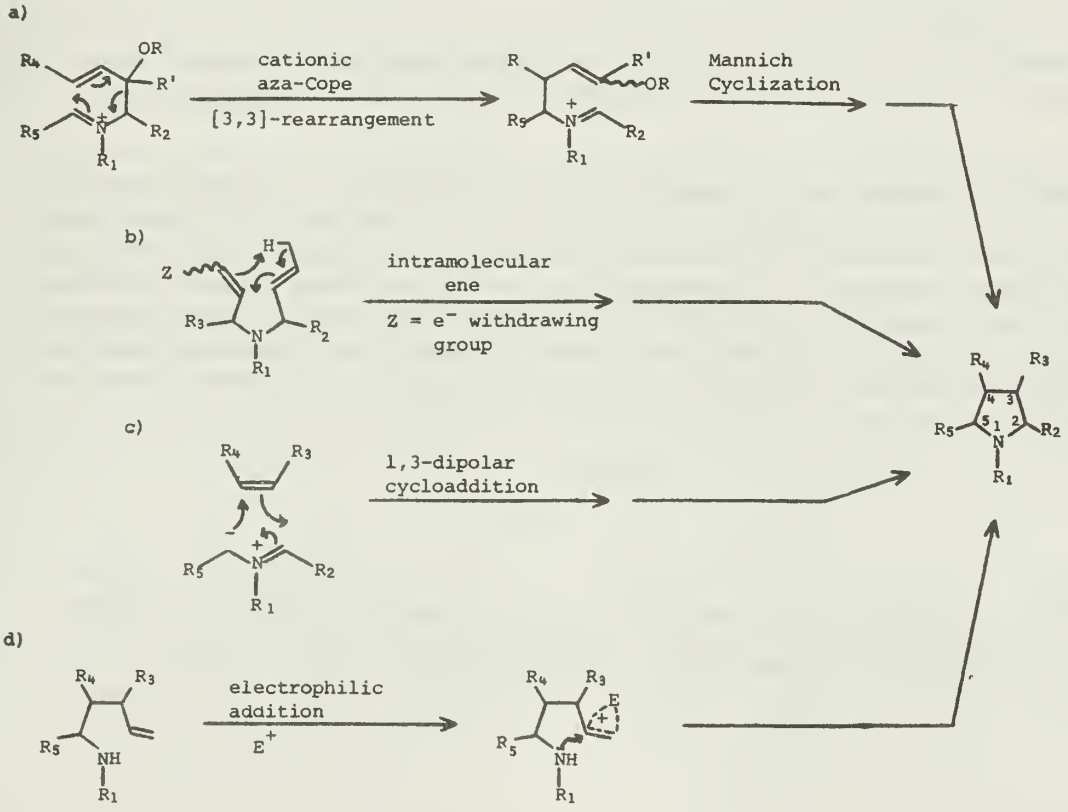
The biological activity of certain polysubstituted pyrrolidines has led to considerable interest in these heterocycles. Several polysubstituted pyrrolidines have been shown to have anthelmintic properties as well as being potent neurotransmitters in mammals, while others are commonly found in the poison glands of certain ant species.[1] Polysubstituted pyrrolidines not only compose an important class of natural products, but, with the correct substituents, can be important intermediates in the synthesis of more complex alkaloids.[2]

In recent years, due to their biological and synthetic utility, a wide variety of synthons for polysubstituted pyrrolidines have been reported.[3] The main concern of this seminar will be to present the recent synthetic approaches to substituted pyrrolidines, concentrating on the methods which offer some degree of regio- and/or stereoselectivity resulting from the formation of the 5-membered ring.

General

Scheme I illustrates four synthetic pathways, a)-d), that lead to pyrrolidines. The cationic aza-Cope rearrangement (2-azonia-[3,3]-sigmatropic rearrangement) used in tandem with a Mannich cyclization (Scheme I, a) yields a wide range of 3-acylpyrrolidines under extremely mild conditions. The

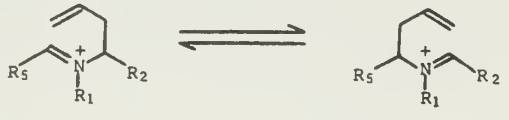
Scheme I



intramoleuclar ene reaction (Scheme I, b) allows the appropriate 1,6-diene to be cyclized at modest temperatures (130-180°C) to give the corresponding pyrrolidines. This method allows a good deal of control over the stereochemistry at C-3 and C-4. The addition of mild Lewis acids to the 1,6-dienes greatly accelerates the intramolecular ene cyclization, which allows cyclization to occur at -35°, serving to enhance further the stereoselectivity of the reaction. The 1,3-dipolar cycloaddition reaction has also been applied to the synthesis of pyrrolidines (Scheme I, c) by allowing various azomethine ylides to react with activated[20] and (in certain cases) unactivated dipolarophiles.[22-23] The degree of regio- and stereospecificity in the 1,3-dipolar cyclizations seems to be dependent on the substituents of the azomethine ylides and the reactivities of the dipolarophiles.[21] Furthermore, pyrrolidines have been synthesized by the electrophile-promoted cyclization of suitably disposed amino-alkenes (Scheme I, d). In this process the lone pair of electrons on nitrogen attacks the more stable carbonium ion, yielding the 5-membered heterocycle. The stereoselectivity at C-2 is affected by the substituents at N-1 and C-5 and by the types of electrophiles used to promote the cyclization. All of the processes mentioned are methods in which the key step is the formation of the 5-membered heterocylic ring, giving polysubstituted pyrrolidines with considerable regio- and stereospecificity.

Pyrrolidines via Tandem Cationic Aza-Cope Rearrangement - Mannich Reaction

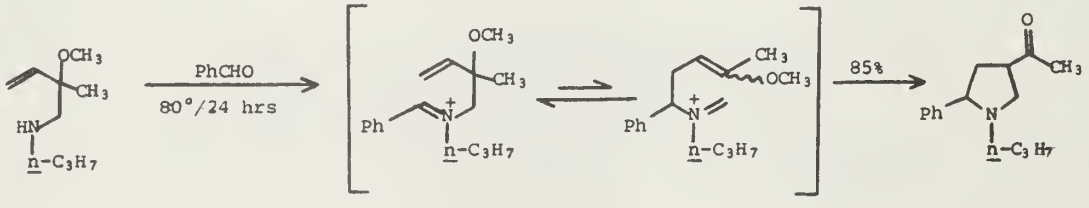
The cationic aza-Cope rearrangement has received considerable attention since it was first described in 1950 by Geissman.[4] Particularly attractive aspects of the cationic aza-Cope rearrangemnt are that the reaction usually occurs at or slightly above temperatures, and a wide range of iminium ions



suitable for rearrangement may be made.[5] Most applications of the cationic aza-Cope reaction in synthesis were directed at benzoheterocycles, where the rearrangement was made essentially irreversible by aryl conjugation (R_2 = aryl).

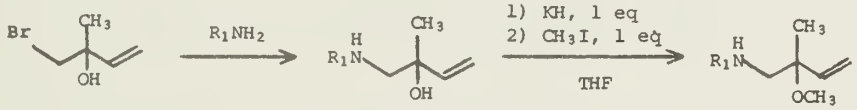
Recently, Overman and co-workers have exploited the cationic aza-Cope reaction used in tandem with a Mannich trap to produce 3-acylpyrrolidines (Scheme II).[6-7] The strategy was to incorporate a nucleophilic agent that is masked in the starting iminium ion, but upon [3,3]-sigmatropic rearrangement irreversibly captures the desired (and sometimes less stable) iminium ion isomer via a Mannich cyclization. Utilization of this method allows the formation of a variety of substituted 3-acylpyrrolidines from the reaction of 2-alkoxy (or hydroxy)-3-alkenamines with aldehydes or ketones under extremely mild conditions.

Scheme II



The formation of the requisite 2-methoxy (or hydroxy)-3-alkenamines, 1a or 1b, can be accomplished (Scheme III) in 60-90% yield and in multi-gram quantities by the action of a primary amine on isoprene-1-oxide, which is formed in situ from 1-bromo-2-methyl-3-buten-2-ol.[8] The reaction between the primary amines and isoprene-1-oxides takes place at moderate temperatures (60-100°) and produces only the regioisomer shown. Selective O-alkylation to produce 1b is achieved by using 1 equivalent of potassium hydride with 1 equivalent of methyl iodide in tetrahydrofuran at room temperature.[9]

Scheme III

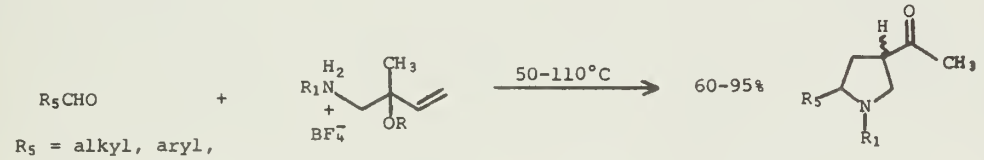


1a: R = alkyl, aryl, benzyl, H

1b

The reaction of salts of 1a and 1b with unhindered aldehydes gives good yield of 1- and 5-substituted 3-acetylpyrrolidines 3 in a one-step process shown in Scheme IV. The amine tetrafluoroborate salts 2a or 2b, or 0.9 equivalents of camphorsulfonic acid with the free amines 1a or 1b, may be used with aldehydes to provide 3 in 60-95% yield. The reaction proceeds in a wide range of solvents but toluene or benzene is most commonly used. The pyrrolidines 3 were obtained as a mixture of acety epimers (1:1 to 1:3), their ratio being highly dependent on the reaction conditions. Yields of 3 and reaction rates were generally higher using hydroxyalkenamines 2a rather than alkoxyalkenamines 2b. The reactions were also notably slower with aromatic amines.

Scheme IV



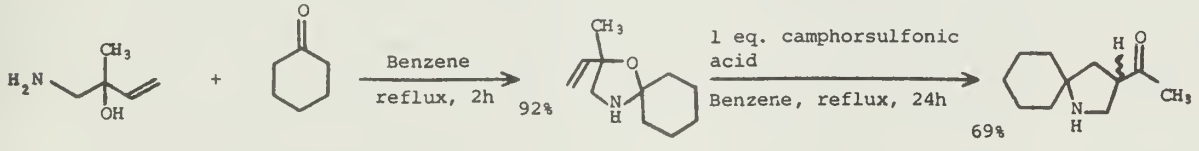
2a: R = H

2b: R = CH3

3

Attempts to use either hindered aldehydes or ketones with the secondary amine salts 2a according to Scheme IV failed. Addition of hindered aldehydes or ketones could only be accomplished if a primary alkenamine 1a, (R_1=H) was employed. However, the reaction of ketones with the primary alkenamine did not proceed in a one-step fashion (Scheme IV), but rather proceeded in a two-step process through an oxazolidine intermediate followed by an acid-catalyzed rearrangement of the oxazolidine to give the corresponding pyrrolidine (Scheme V).

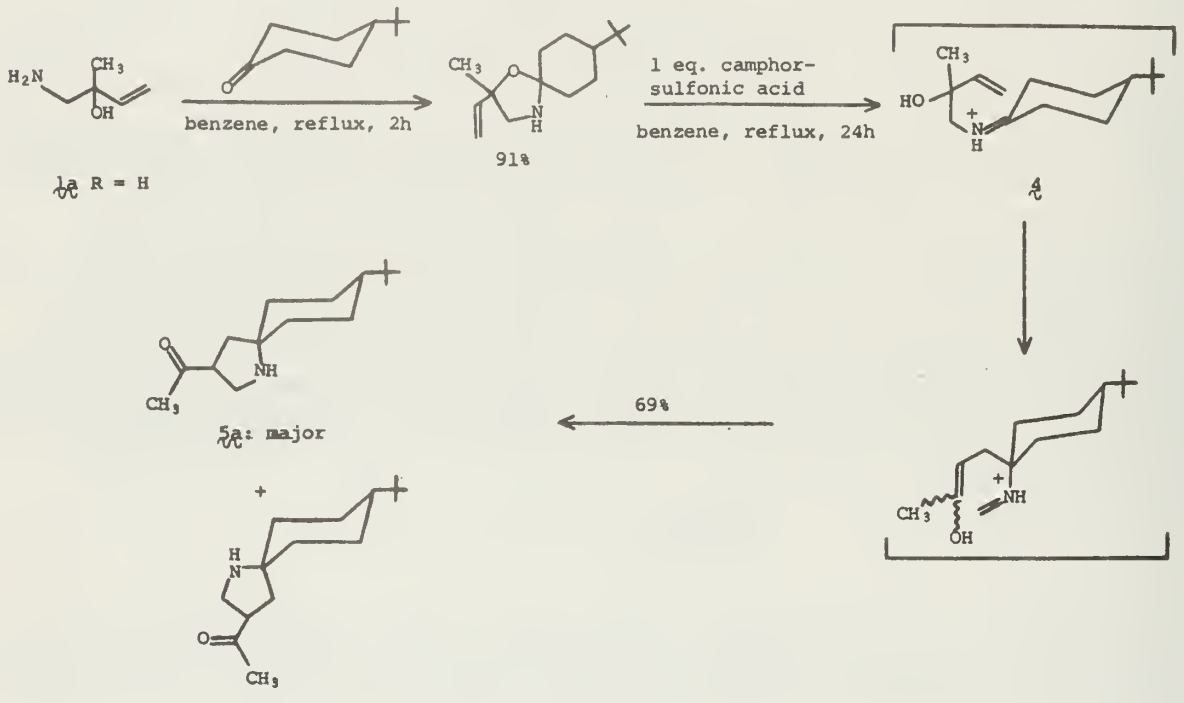
Scheme V



This two-step process is an efficient method of synthesis of 1-azaspiro[4.5]-decanes (>50% yield from cyclohexanones), but is less effective with other cyclic ketones. 3-Formylpyrrolidines can also be produced in this manner by employing 2-hydroxy-3-butenamines rather than the 2-hydroxy-2-methyl-3-butenamines.

A high level of stereocontrol is usually observed in [3,3]-sigmatropic rearrangements.[10] Therefore, it is not surprising that when the primary alkenamine 1a, (R_1=H) was allowed to react with 4-tert-butylcyclohexanone a 92:8 mixutre of stereoisomeric 1-azaspiro[4.5]decanes was obtained (Scheme VI).

Scheme VI



1a R = H

5a: major

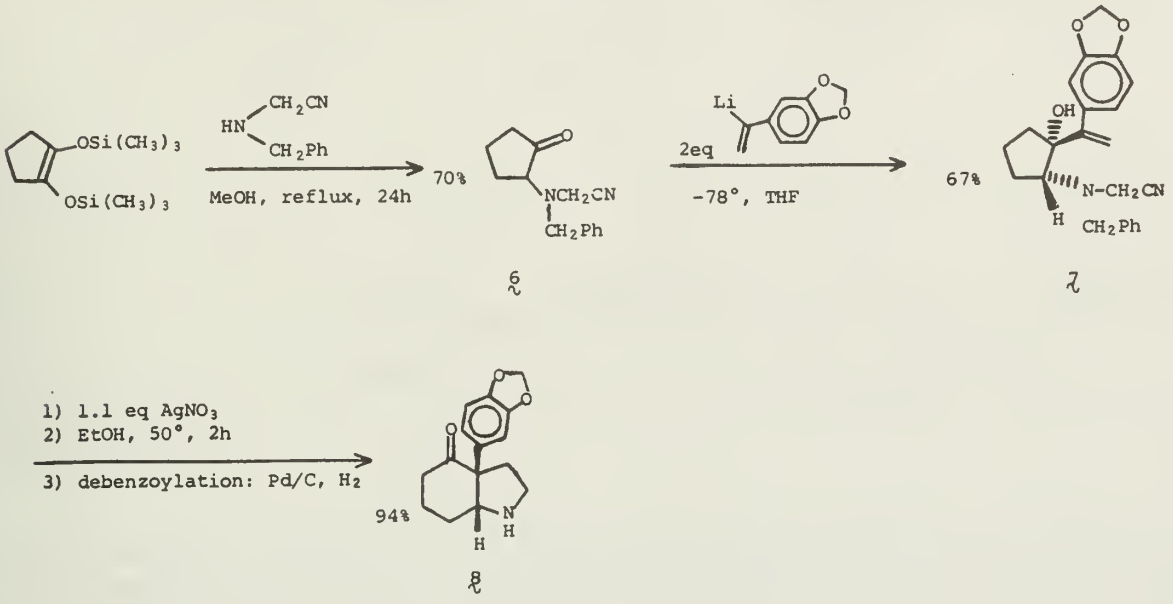
5b: minor

The stereochemical assignments were based on lanthanide-induced shift experiments and N-benzylation rate studies. Presumably the preponderance of the product stereoisomer 5a (shown in Scheme VI) is the result of the [3,3]-sigmatropic rearrangement of the iminium ion 4 taking place preferentially from the equatorial position as shown. The degree of stereochemical control in this example is higher than previously observed from analogous Claisen or ortho-ester Claisen rearrangements.[11]

Overman has recently extended this synthetic methodology to the synthesis of cis-3a-aryl-4-oxooctahydroindoles.[2] Outlined in Scheme VII is the synthesis of 3a-(3,4-(methylenedioxy)phenyl)-4-oxo-cis-octahydroindole, 8, which was a key intermediate in the Whitlock and Smith synthesis of (±)-crinine.[12] Treatment of the readily available 1,2-bis[(trimethylsilyl)oxy]cyclopentene with benzyl(cyanomethyl)amine afforded amino ketone 6. Reaction of 6 with 2 equivalents of [1-(3,4-methylenedioxy)phenyl)ethenyl] lithium at -78° in tetrahydrofuran yielded a 14:1 mixutre of alcohol 7 and the corresponding trans-isomer. Treatment of 7 with 1.1 equivalents of silver nitrate at 50° in ethanol, followed by debenzoylation, gave 8 in 94% yield from 7. The stereospecific formation of 8 from 7 is due to the existence of a single

"chair-type" transition state when the amine and vinyl groups are trans in the cyclopentanol. The trans-isomer of 7 is much less stereoselective in the formation of 8 since there are four distinct ways to bring the cis-oriented vinyl and azavinyl groups within bonding distance.

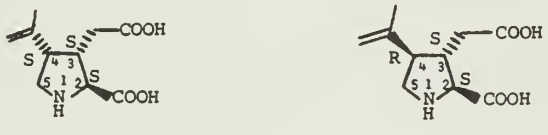
Scheme VII



6 7 8

Pyrrolidines via the Intramolecular Ene Reaction

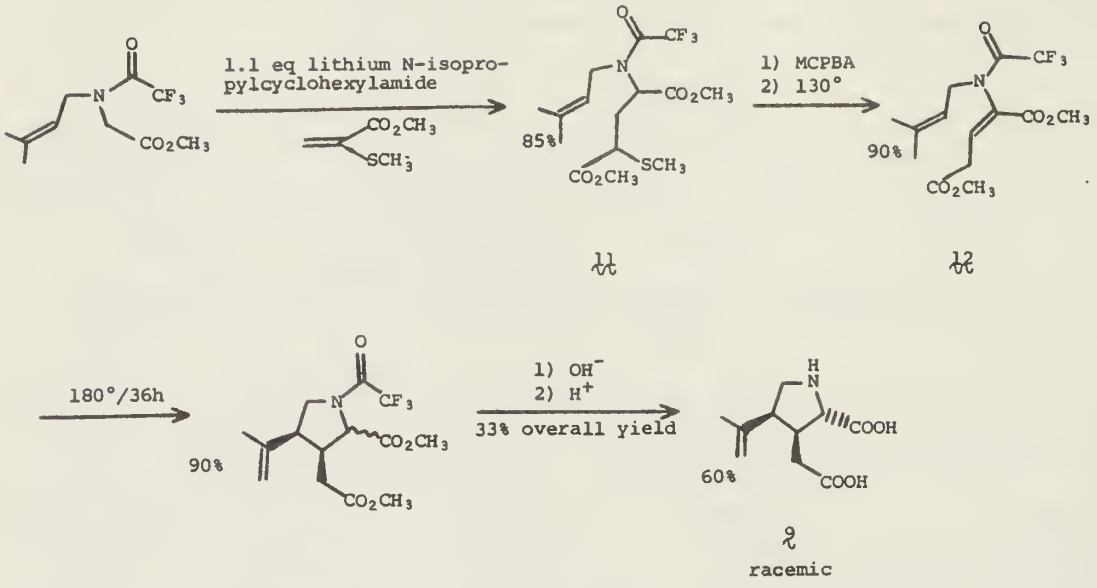
Most applications of the intramolecular ene reaction to the synthesis of polysubstituted pyrrolidines have been directed toward the production of the potent neurotoxins and anthelmintics (-)-α-kainic acid, 9, and (+)-α-allokainic acid, 10, which are natural products isolated from certain marine algae.[13] The intramolecular ene reaction seemed to be well suited for the synthesis of 9 and 10 (which differ only in the relative configurations at C-3 and C-4) due to earlier investigations which indicated that the stereochemistry at C-3 and C-4 in the resulting 5-membered ring could be controlled.[14-15] Oppolzer successfully exploited the intramolecular ene reaction to synthesize 9 and 10 in racemic and optically active forms.



9 10

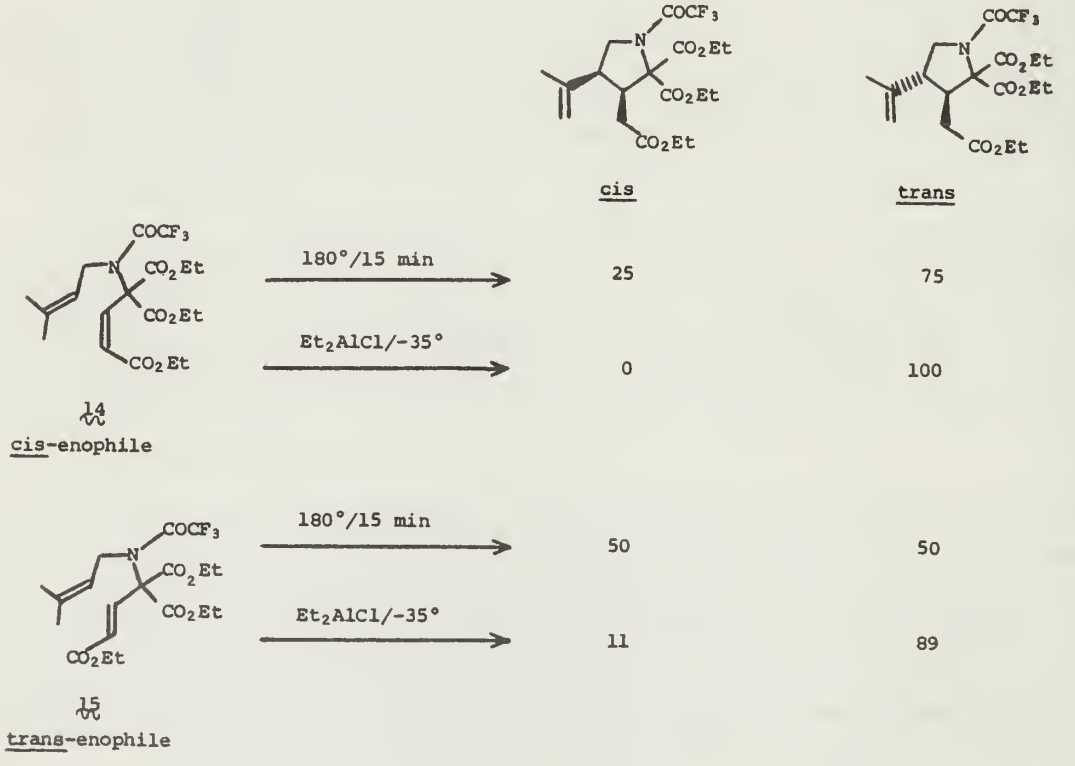
The racemic synthesis of α-kainic acid is outlined in Scheme VIII.[16] The thioether 11, when oxidized and subjected to thermal desulfenylation conditions, initially formed the 1,6-diene, which isomerized to the 1,5-diene 12. Anticipating the isomerization process to be reversible at high temperature, 12 was heated to 180° for 36 hours to yield (via the intramolecular ene reaction) predominantly the cis-isomer of the diester amide 13. Saponification of the esters and removal of the N-protecting group yielded racemic 9 in 41% overall yield from the starting ester amide.

Scheme VIII



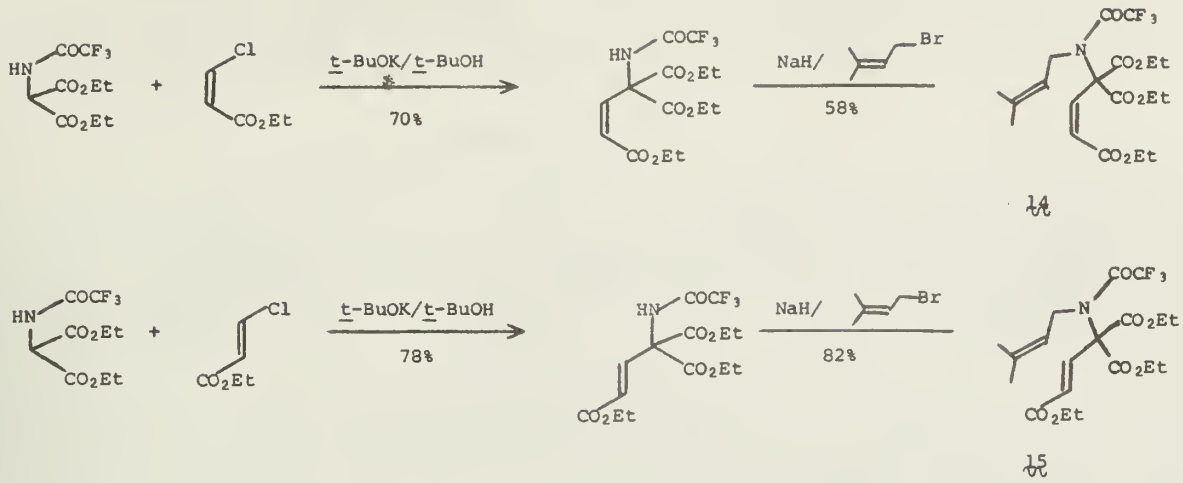
If an efficient synthesis of 10 via the intramolecular ene reaction is to be successfully employed, trans-stereochemistry at C-3 and C-4 must be obtained. Oppolzer discovered that a preponderance of the C-3, C-4 trans-pyrrolidine is obtained if a gem-diester 1,6-diene is used. The cis/trans ratio was also highly affected by the geometry of the enophile (Scheme IX).

Scheme IX



The synthesis of the cis- and trans-enophiles are summarized in Scheme X. The addition of amild Lewis acid (Et_2AlCl) to the diene caused acceleration of the ene reaction and provided even larger excesses of the trans-isomer.[17] Oppolzer

Scheme X

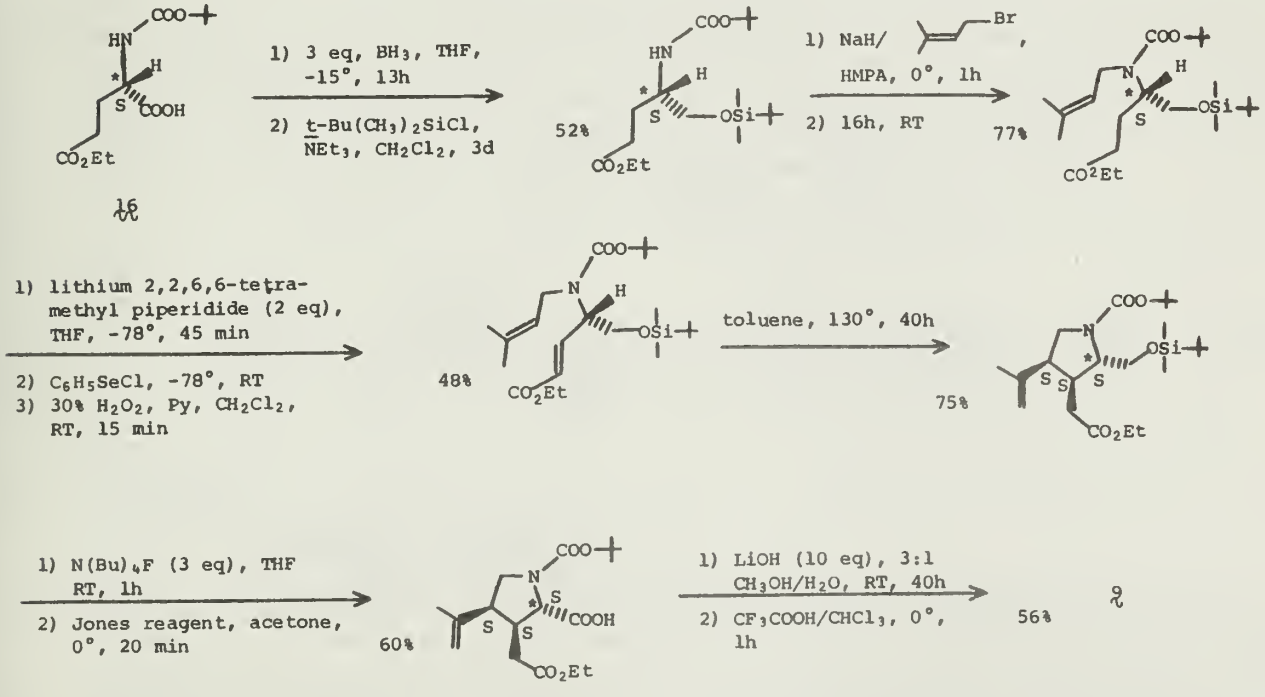


also was able to produce stereoselectively racemic 10 in 57% yield from the cis-enophile 14 by utilizing the optimum conditions for the production of the trans-isomer in Scheme IX.

The results in Scheme IX (for the uncatalyzed ene reaction) may be rationalized by examination of transition state geometries. However, in reference to the Lewis acid-catalyzed reaction, it is not conclusively known what effect Lewis acids have on the transition states in ene reactions. The authors suggested that the Lewis acid, by complexation to the amide and ester functionalities, increases their steric bulk and serves to increase stereochemical bias in the transition states.

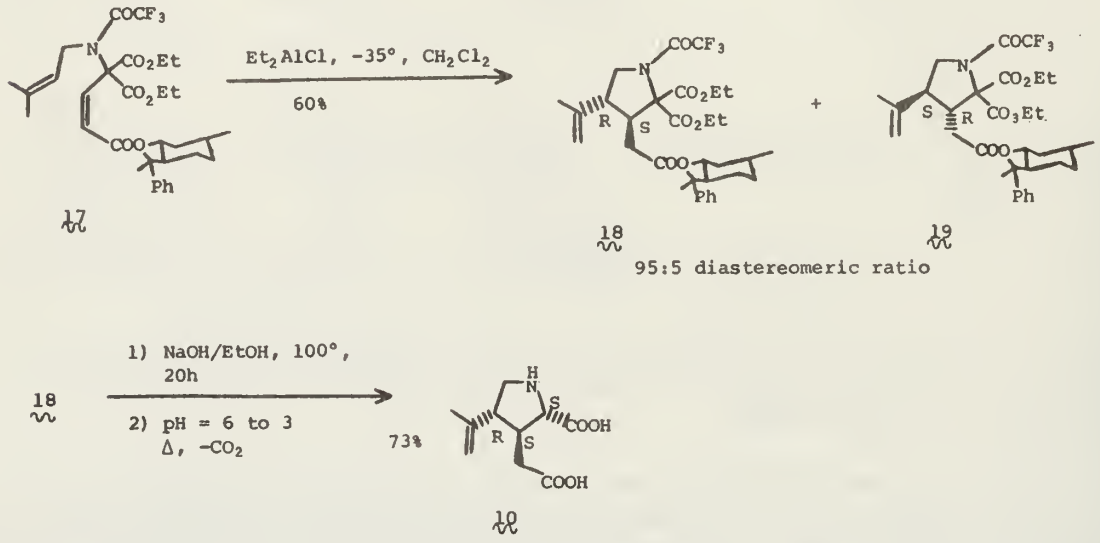
Most recently Oppolzer has devised enantioselective syntheses for 9 and 10 via the intramolecular ene reaction. The naturally occurring enantiomer (-)-α-kainic acid 9 was produced in 5% overall yield from γ-ethyl-(S)-(+)-glutamate (Scheme XI).[18] The selective reduction of the α-carboxyl group of

Scheme XI



16 with diborane, followed by silylation of the resulting primary alcohol, was needed to avoid loss of chirality due to thermal olefin migration, analogous to the process which produced 12. (+)-α-allokainic acid was synthesized enantioselectively according to Scheme XII.[19] Treatment of the cis-

Scheme XII

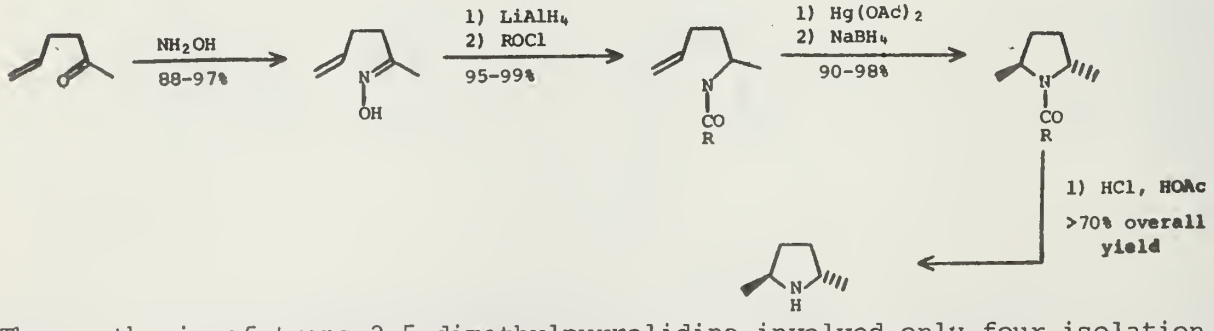


phenylmenthyl ester 17 (prepared by analogy to the preparation of 14 using (-)-8-phenylmenthol and cis-β-chloroacrylic acid) with 3 equivalents of diethylaluminum chloride at -35° gave diastereomers 18 and 19 in a 95:5 ratio (60% chemical yield from 17). Saponification of 18 followed by successive decarboxylation of the non-isolated malonic acid gave enantiomerically pure 10 in 73% yield from 18.

Pyrrolidines via Cyclizations of Acylamino-alkenes

The electrophile-promoted cyclization of δ-alkenyl amine derivatives has mainly been used in the synthesis of trans-2,5-dialkylpyrrolidines, which are characteristic components in the poison glands of a variety of ant species.[25] A highly stereoselective synthesis of trans-2,5-dialkylpyrrolidines has been accomplished by intramolecular amidomercuration (Scheme XIII).[26] The commercially available ketone was converted into the oxime in 88-97% yield by treatment with hydroxylamine. The oxime was then reduced and direct acylation of the crude amine gave the amide in 95-99% yield. Treatment of the δ-alkenyl-N-acylamine with mercuric acetate in tetrahydrofuran followed by borohydride reduction yielded exclusively the trans-cyclization product in 90-95% yield.

Scheme XIII



The synthesis of trans-2,5-dimethylpyrrolidine involved only four isolation steps with minimal purification and proceeded in greater than 70% overall yield. The cyclizations of analogous δ-alkenyl-N-alkylamines via the intramolecular amidomercuration process yielded much less regio- and stereoselectivity.[27]

The stereoselectivity in the cyclization process is rationalized by the preference for a "chair-like" transition state with an equatorial methyl group. Other electrophilic agents such as benzeneselenenyl chloride[28] (in the presence of silica gel), iodine,[29] and N-phenylselenophthalimide[30] do not impart nearly as much stereoselectivity in the resulting pyrrolidines as mercuric acetate.

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TRIPLEXES IN ORGANIC PHOTOCHEMICAL REACTIONS

Reported by Barbara Goodson February 13, 1984

Excimers, (AA)*, and exciplexes, (AB)*, which are electronically excited complexes formed between two molecules, are well known to exist and participate as intermediates in photochemical reactions.[1] These species may react with ground-state molecules to form excited-state triple complexes (AAB)* termed triplexes[2] or exterplexes.[3] Formation of triplexes is accompanied by a decrease in exciplex fluorescence intensity and usually the appearance of a new fluorescent band shifted bathochromically from the exciplex emission.[4] In some cases, double exponential decay of the exciplex fluorescence upon quenching may be observed.[5] Molecular orbital calculations,[6] studies of the properties of carefully designed cyclophanes,[7] and experiments investigating dipole moments using solvent effects[2] have firmly established a non-symmetrical structure for a number of triplexes (i.e, AAB, not ABA). Triplexes which have been detected include those formed from intramolecular exciplexes of cyanoanthrylnaphthalenes with various pyridines,[5,8] from aromatically substituted propylenediamines,[9] exciplexes of aromatic hydrocarbons and amines with either amines or aromatic hydrocarbons,[10] aromatic nitrile/imidazole exciplexes with various imidazoles,[11] the exciplex of 9,10-dichloroanthracene and 2,5-dimethyl-2,4-hexadiene with the same diene,[12] poly-N-vinylcarbazole excimer with benzanthrone,[13] and the naphthalene/1,4-dicyanobenzene exciplex with naphthalene.

The fact that exciplexes are quenched upon formation of triplexes has been used as a method for establishing the intermediacy of exciplexes in reactions.[14] The attenuation in product yield upon quenching of exciplexes by various electron donors suggested exciplex intermediacy in the photocycloaddition of phenanthrene to dimethyl fumarate,[15,16,17] 9,10-dichloroanthracene to 1,3-cyclohexadiene,[18] and 9-cyanoanthracene to substituted β-methylstyrenes.[19]

Triplexes have been implicated as intermediates in several reactions. The most detailed study involved the photodimerization of anthracene in benzene in the presence of N,N-dimethylaniline (DMA). In the absence of DMA, the reaction proceeds via the anthracene excimer (AA)* to yield the photodimer 9,10-dihydro-9,10-[9',10'-dianthraceno]anthracene (A_2) as the sole product.[20] Yang and colleagues[21] found at high concentration of DMA and relatively low concentration of anthracene little or no photodimer is formed and the major products are 9-N-(N-methylanilino)-9,10-dihydroanthracene and 9,9',10,10'-tetrahydro-9,9'-dianthryl. At either low DMA concentration or high concentrations of both anthracene and DMA, A_2 and 9,9',10,10'-tetrahydro-9,9'-bianthryl are the products. Their kinetic and spectroscopic data and those of Saltiel and coworkers[22] suggested that at low DMA concentration (AA)* and the anthracene/DMA exciplex (A:DMA)* may interact with a molecule of DMA or anthracene, respectively, to form the triplex (A_2:DMA)*, which gives A_2. At high DMA concentrations they postulated that both (A:DMA)* and (A:DMA_2)* proceed to give the DMA-anthracene adduct, while 9,9',10,10'-tetrahydro-9,9'-bianthryl arises from the bimolecular reduction of anthracene by protonated DMA. Although they had no conclusive evidence for the existence of a triplex in these reactions, formation of such a species is consistent with their kinetic data and the observed quenching of the exciplex fluorescence quantum yield and lifetime with increasing DMA concentration. The fact that a triplex between anthracene and N,N-diethylaniline is known[10d] makes the existence of an anthracene/DMA triplex even more plausible. Saltiel and coworkers[23] studied

the photolysis of 9,10-dichloroanthracene in acetonitrile in the presence of 2,5-dimethyl-2,3-hexadiene, which leads to the formation of 9-chloroanthracene and diene-related products. In contrast to the singlet and triplet-sensitized dimerizations of 1,3-cyclohexadiene which produce predominately [2+2] cycloaddition products, Jones, et al.[24] isolated in high yield the [4+2] adducts endo- and exo-dicyclohexadiene from the photolysis of 1,3-cyclohexadiene in methylene chloride in the presence of 9,10-dicyanoanthracene. Both of these reactions are believed to occur via triplex intermediates. The formation of an oxetane from the photolysis of trans-stilbene with dimethyl fumarate in benzene has been explained as proceeding from the interaction of stilbene excimer with ground-state dimethyl fumarate.[25] It has been suggested that this interaction involves a triplex.[1b]

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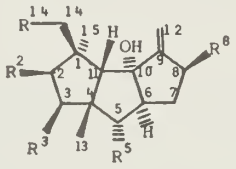
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SYNTHESES OF CAPNELLENE

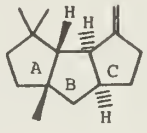
Reported by Dae Yoon Chi February 16, 1984

In 1974, the novel tricyclic sesquiterpene alcohol 1, ($\Delta^{9(12)}$-capnellene-3β,8β,10α-triol) was isolated from the soft coral Capnella imbricata collected off Serwaru, Leti Island, Indonesia, and characterized by the Djerassi and Tursch groups.[1] The skeletal type was given the name capnellane. Over a period of several years, other capnellols, 2-5, were isolated from C. imbricata.[2] These substances may act as chemical defense agents in the coral reef biomass to ward off algal and microbial growth and to prevent larval settlement.

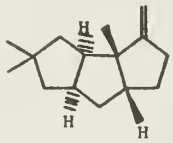
In addition to these alcohols, in 1978 the Djerassi group reported the isolation and structural elucidation of a new sesquiterpene hydrocarbon, $\Delta^{9(12)}$-capnellene, 6, which may be the biogenetic precursor of the alcohols 1-5.[3]



1 $R^2=R^5=R^{14}=H$, $R^3=R^8=OH$
2 $R^2=R^5=H$, $R^3=R^8=R^{14}=OH$
3 $R^2=R^3=R^{14}=H$, $R^5=R^8=OH$
4 $R^3=R^{14}=H$, $R^2=R^9=R^8=OH$
5 $R^3=R^5=R^{14}=H$, $R^2=R^8=OH$



6



7

There are precedents for gaining successful entry to the capnellane ring system because of its relationship to the hirsutanes, e.g., hirsutene, 7, which is found in the fungus Stereum hirsutum. Both structures have the cis, anti, cis-tricyclo[6.3.0.$0^{2,6}$]undecane system. However, the location of the substituents in capnellene so differs from that in hirsutene that intrinsically dissimilar synthetic approaches appear to be required.

Recently, five varied and specific syntheses have been achieved. These include: 1) successive stereocontrolled annulation,[4] 2) an iterative intramolecular type-I "magnesium-ene" process,[5] 3) a biogenetically patterned synthesis from precapnelladiene,[6] 4) an unusual rearrangement from humulene 7,8-epoxide,[7,8] and 5) an intramolecular 1,3-diyl trapping reactions.[9]

Successive stereocontrolled annulation

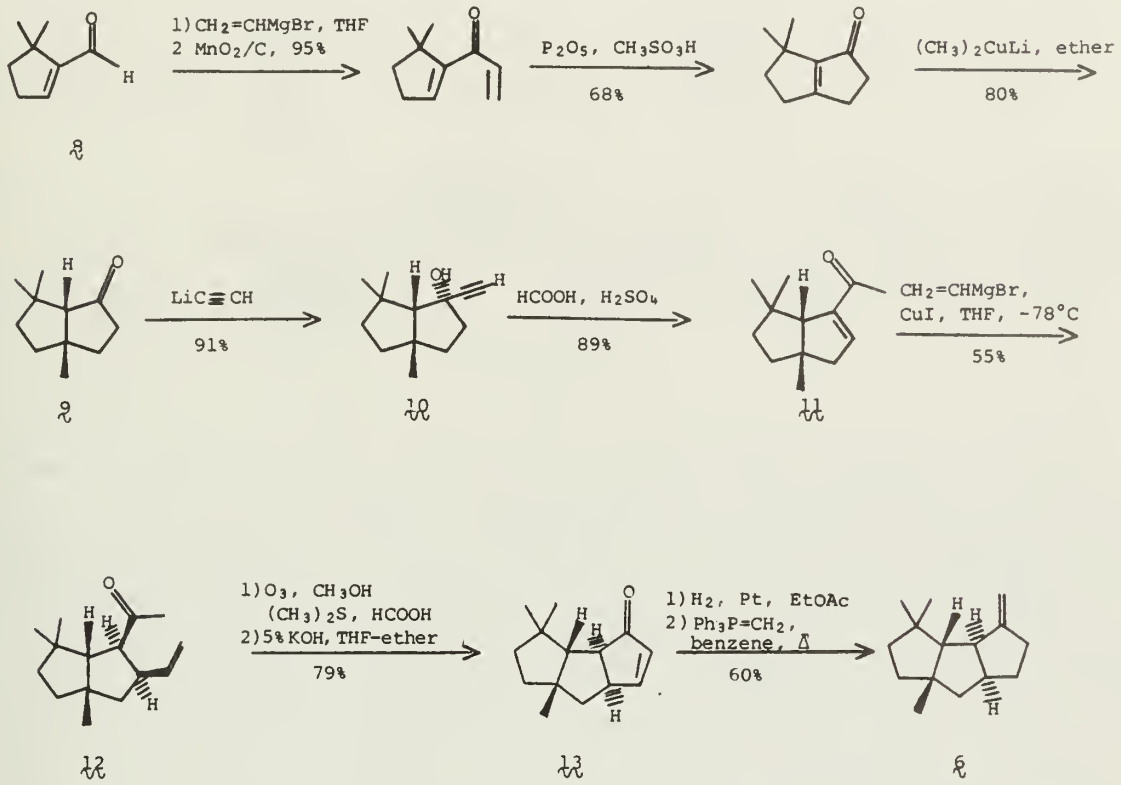
The first stereospecific total synthesis of capnellene, 6, from 5,5-dimethylcyclopent-1-enecarboxaldehyde, 8, was reported by Stevens and Paquette in 1981.[4] Their approach involved successive stereocontrolled annulation.

Addition of vinylmagnesium bromide to aldehyde 8, oxidation by manganese dioxide, Nazarov cyclization with phosphorus pentoxide in methanesulfonic acid, and conjugate addition of lithium dimethylcuprate gave the desired trimethylbicyclo[3.3.0]octanone 9. This bicyclooctanone was condensed with lithium acetylide to arrive at propargylic alcohol 10. Rupe rearrangement gave rise to α,β-unsaturated ketone 11 through a dehydration-hydration sequence. The strong preference for formation of the less substituted enone with formic acid and a trace of sulfuric acid was noteworthy. Treatment of enone 11

with vinylmagnesium bromide in the presence of cuprous iodide afforded a single isomer of vinylated ketone 12. Ozonolysis, cyclization of the keto aldehyde, catalytic hydrogenation, and Wittig methylenation gave racemic $\Delta^{9(12)}$-capnellene, 6.

The synthesis required 9 steps and the overall yield was 11% (from 5,5-dimethylcyclopent-1-enecarboxaldehyde, 8).

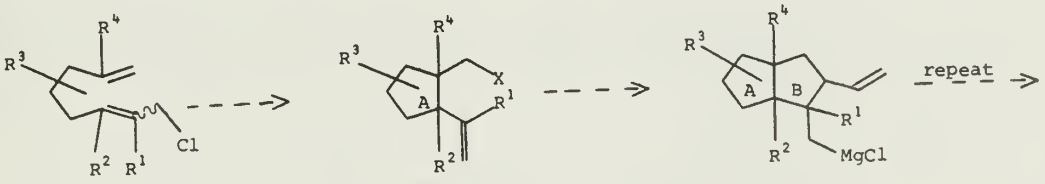
Scheme I



An iterative intramolecular "magnesium-ene" process

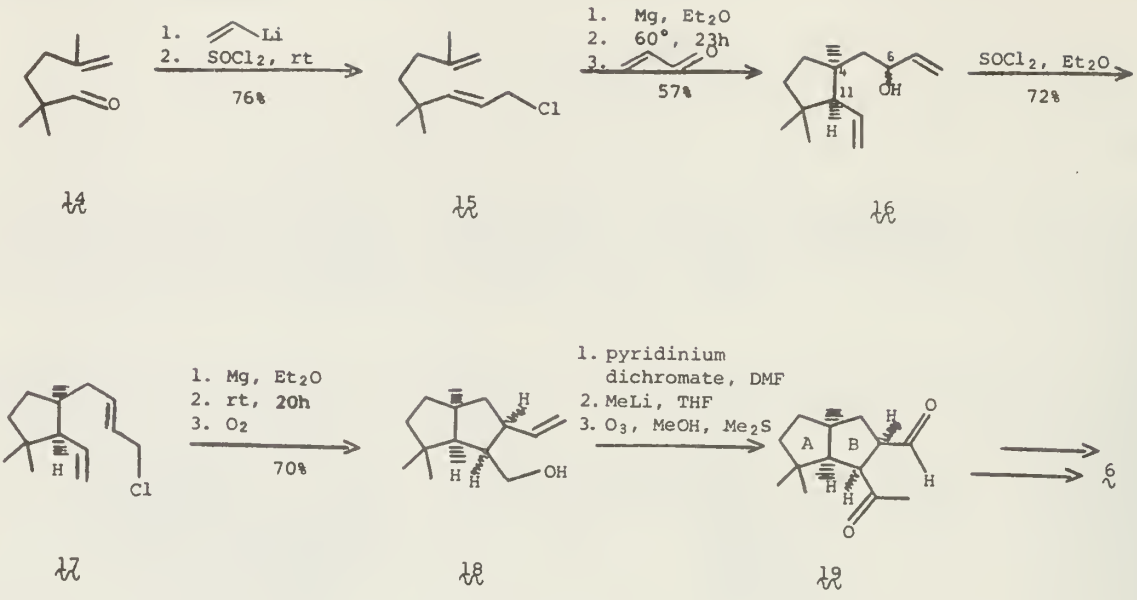
Oppolzer and Bättig used the intramolecular ene reaction involving allylic Grignard reagents and olefins for the synthesis of capnellene.[5] In order to assemble rapidly a polycyclopentanoid system, they were intrigued by the idea of using a repetitive "magnesium-ene" process as in Scheme 2. By using the intramolecular "magnesium-ene" reaction of a 2,7-octadienylmagnesium halide, they could overcome the problems of efficiency and regiochemistry inherent in a bimolecular process.

Scheme II



a: X = MgCl
b: X = CHOH—CH=CH2
c: X = CH=CH—CH2—Cl

Scheme III

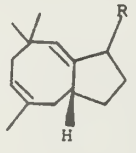


14 15 16 17 18 19 6

Starting from the known aldehyde 14, rings A and B of capnellene were assembled by a sequence of two "magnesium-ene" reactions (Scheme III). It is worth noting that the first key step, 15→16, involved the first known successful "magnesium-ene" addition to a non-activated 1,1-disubstituted olefin. This allowed closing of the congested C-4, C-11 bond[7] with high stereochemical control. The Grignard reagent prepared from 17 cyclized smoothly at room temperature, and the product was trapped with oxygen to give a 3:2-mixture of cis (two isomers) and trans (two isomers) alcohols 18, stereoisomeric at C-6 and C-10.[7] Oxidation of the primary alcohols 18 to the acids, followed by addition of methyllithium and ozonolysis afforded the keto aldehydes 19. The critical aldolization conditions made both isomers of 19 into the same cis, anti, cis-tricyclo[6.3.0.$0^{2,6}$]undodecenone, 13, via base-induced epimerization at C-6 and/or at C-10. The complete synthesis of 6 required 15 steps from aldehyde 14 and proceeded in 5% overall yield.

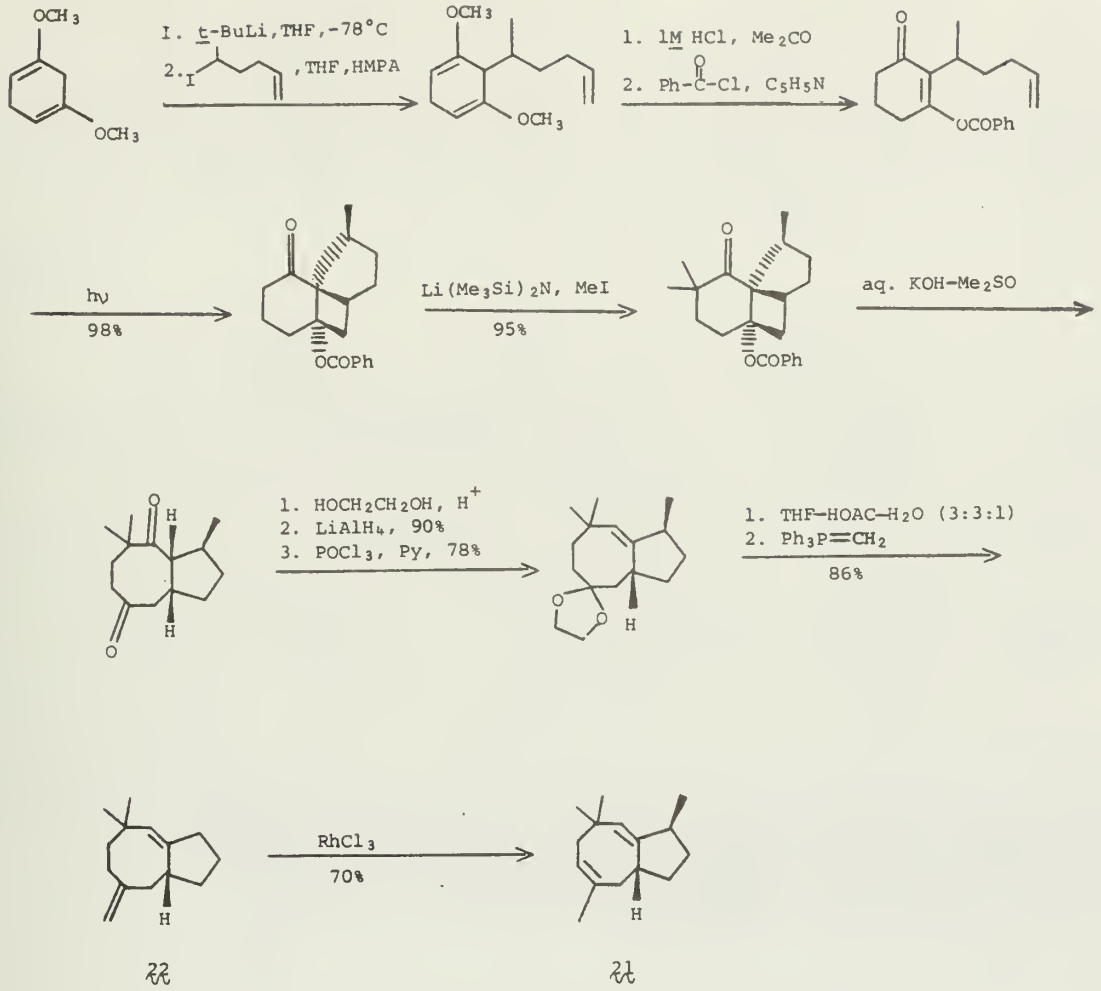
A biogenetically patterned synthesis from precapnelladiene

In 1979, precapnelladiene, 20, which has an uncommon fused 5- and 8-membered ring system, was isolated by the Djerassi group, and this compound is thought to be a key biosynthetic precursor of the unique tricyclic capnellane group found in the same marine animal.[10] A biogenetically patterned synthesis through the sesquiterpene precapnelladiene, 20, thus is , another approach toward synthesizing capnellene.[6,11] In 1980, Birch and Pattenden reported the total synthesis of epi-precapnelladiene, 21, by a highly regio- and stereoselective intramolecular photocycloaddition reaction, elaborating the fused 5,8-ring system as shown in Scheme IV.[11]



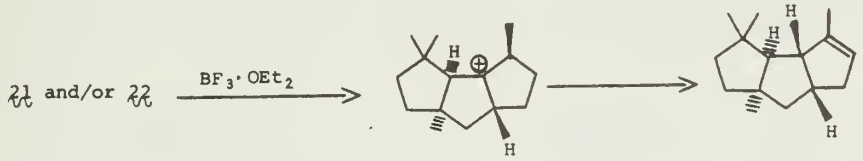
20 R=≡Me
21 R=═Me

Scheme IV



22 21

The transannular cyclization of synthetic epi-precapnelladiene, 21, and its exo-methylene isomer 22 to the capnellene carbon framework were achieved with boron trifluoride etherate via the same carbocation intermediate, 23.[6]

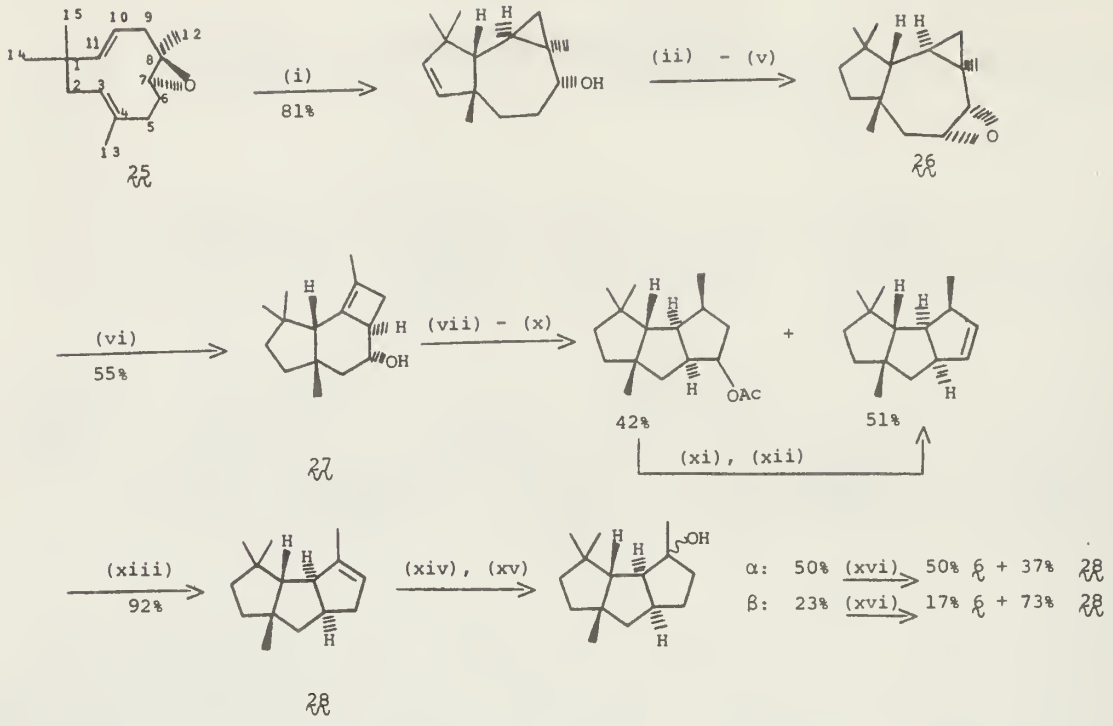


23 24

An unusual rearrangement from humulene 7,8-epoxide

Another biogenetically patterned synthesis of capnellene from humulene, which may be the ultimate source of capnellene, was reported by Matsumoto, et al.[8] The chemical conversion of humulene to capnellene involved what was described as an apparent methyl group migration in the key step, the rearrangement of epoxide 26 on treatment with trimethylsilyl triflate to give 27 via a cyclopropane sliding mechanism (Scheme V). $\Delta^{9(12)}$-Capnellene, 6, was prepared in 16 steps in 10% yeild from humulene 7,8-epoxide, 25 (assuming quantitative yields in steps (v) and (xiv).

Scheme V

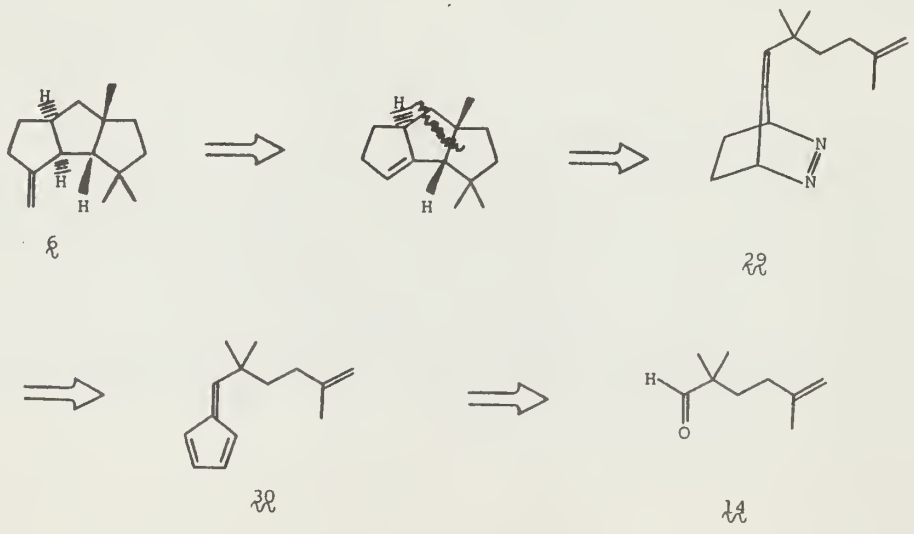


(i) TMSOTf, 2,6-lutidine, toluene (ii) H_2, PtO_2, AcOEt, 99% (iii) Jones reagent, 97% (iv) $TsNHNH_2$, EtOH, Δ, 1 h, then n-BuLi, THF, rt, 40 min, 85% (v) mCPBA (vi) TMSOTf, 1N HCl (vii) H_2, PtO_2, EtOH, 98% (viii) Jones reagent, 98% (ix) $Li(s\text{-}Bu)_3BH$, 97% (x) MsCl, N,N-dimethyl-2-aminopyridine (DMAP), NaOAc, AcOH (xi) $LiAlH_4$, 99% (xii) MsCl, DMAP, then basic alumina, 77% (xiii) $RhCl_3$, EtOH, (xiv) mCPBA (xv) $LiAlH_4$ (xvi) Δ, 1,2,3,3,3-pentafluoropropenyldiethylamine.

An intramolecular 1,3-diyl trapping reaction

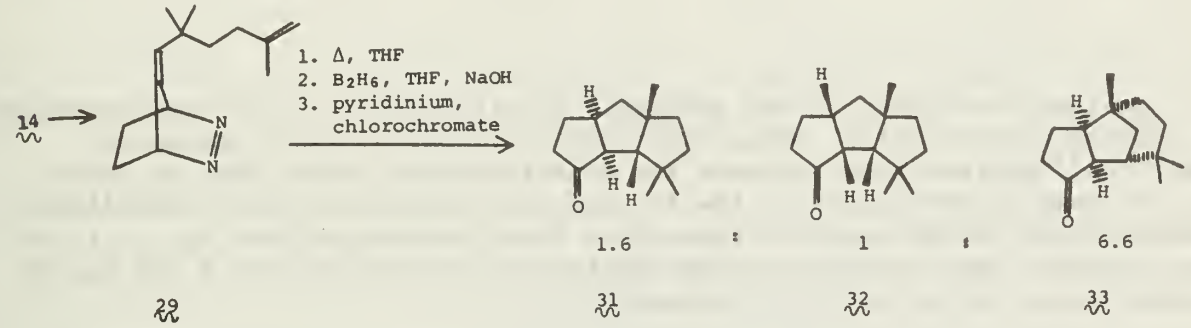
In the last approach, Little and coworkers have tackled the problem from a significantly different point of view. An intramolecular 1,3-diyl trapping reaction constituted the cornerstone of their strategy to achieve the total synthesis of capnellene.[9] This methodology has also been used for the synthesis of hirsutene.[12] The retrosynthetic analysis is shown in Scheme VI.

Scheme VI

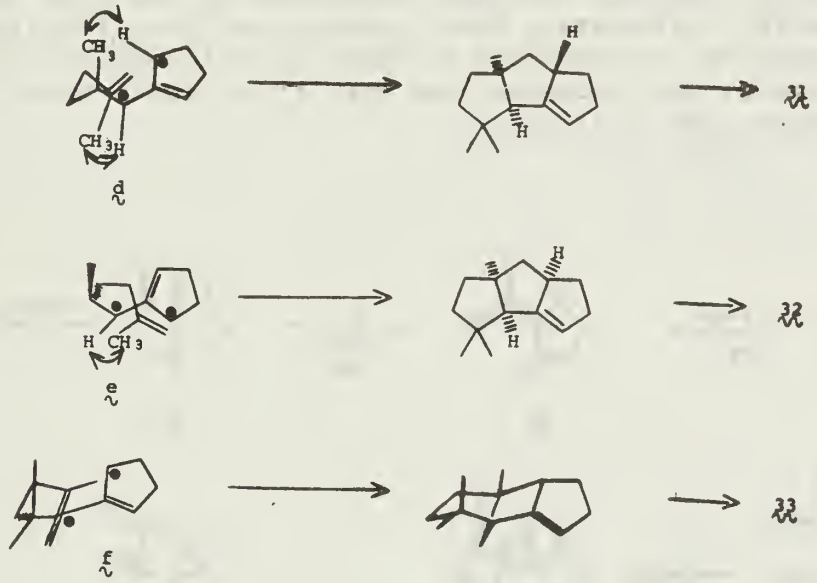


A Diels-Alder reaction between dimethyl azodicarboxylate and fulvene 30 (prepared from the aldehyde 14 and lithium cyclopentadienide), selective reduction of the endocyclic olefin using diimide, saponification, and oxidation provided bicycloazo compound 29. Refluxing the diazene 29 in THF accomplished an intramolecular diyl trapping reaction (Scheme VII) via the diyls d, e, and f (Scheme VIII). In situ hydroboration-oxidation produced ketones 31, 32, and 33 in a ratio of 1.6:1:6.6 (total 56% from 29). The ketone 31 was transformed unambiguously by a simple Wittig reaction into capnellene.

Scheme VII

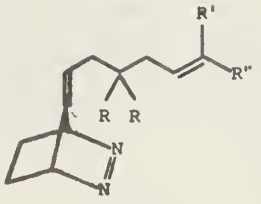


Scheme VIII



In comparison with other intramolecular trapping reactions used in the preparation of hirsutene and related compounds (Table I), the amount of the desired cis, anti ring-fused product was surprisingly and disappointingly low.

Table I

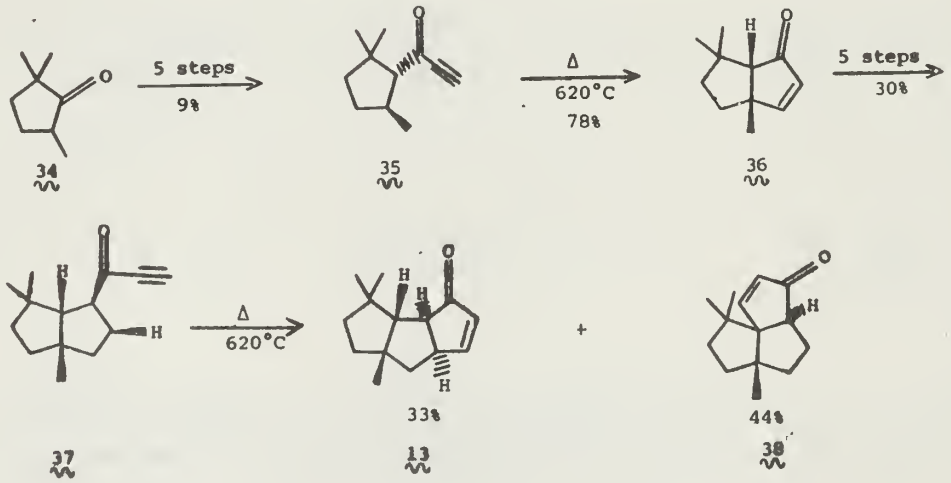


R	R'	R''	yield	anti:syn
CH_3	H	$COOCH_3$	87	9:1
CH_3	$COOCH_3$	H	85	3:1
H	H	$COOCH_3$	85	7:1

On the other hand, in the synthesis of hirsutene 11 steps were necessary to add the angular methyl group after the intramolecular diyl trapping reaction,[12] whereas this sequence for capnellene was short, easy to scale up, and readily modified to allow for the construction of other capnellenes. Consideration of the possible transition state representations (d, e, f) of the trapping reaction suggested the desired product arose from a low energy extended quasi-chair form (d) (Scheme VIII).

In addition to these five target-oriented syntheses, the construction of the capnellene skeleton has also proved useful for testing new synthetic utility of the α-alkynone cyclization by applying it to the preparation of capnellene.[13] Their approach was based on two key intermediates, 2-cyclopentenones 36 and 13, obtained from the α-alkynones 35 and 37 by gas-phase pyrolysis (Scheme IX). Ultimately, their interest was in applying the α-alkynone cyclization to the synthesis of other natural products. However, for capnellene itself, this sequence gave only a 0.6% yield (from 2,2,5-trimethylcyclopentanone, 34) in 14 steps.

Scheme IX



Summary

The capnellanes form an interesting class of marine triquinane sesquiterpene alcohols and hydrocarbons. Five total syntheses of $\Delta^{9(12)}$-capnellene, which is the parent hydrocarbon of several oxygenated capnellanoids, have been described briefly. These approaches can also be applied to the synthesis of capnellane triols and tetrols and other natural products with similar ring systems.

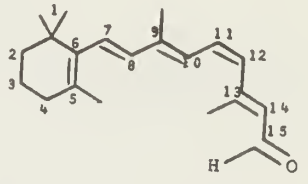
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VISUAL PIGMENT ANALOGUES: THEIR SYNTHESIS AND USE IN OPSIN BINDING-SITE ELUCIDATION

Reported by Stephanie J. Brandes February 20, 1984

In the back of the eye, the retina contains the molecules most intimately involved with the variety of events which enable us to see. These molecules are called visual pigments because they are colored. One such pigment is rhodopsin. It consists of the chromophore 11-cis-retinal (1) bound to the membrane protein opsin.



1

Many studies have been undertaken to determine the exact nature of the retinal-opsin interaction. An excellent review of the progress made through 1980 is available.[1] It has been determined that the primary bond is a Schiff's base linkage connecting the chromophore's aldehyde to an ε-amino group of a lysine residue.[1,2] A question remains, however, as to how the rest of the chromophore fits into the opsin binding site. An indirect method of probing the additional opsin-retinal interactions involves the formation of artificial visual pigments using opsin and retinal analogues with ring or side-chain modifications. The synthesis of these analogues[3] and the information concerning the opsin binding site obtained from the corresponding photosensitive pigments will be discussed here.

Stereoisomers

Nearly all of the sixteen possible stereoisomers of retinal have been isolated. Earlier attempts to synthesize the various isomers consisted of irradiating all-trans retinal in polar and non-polar solvents and isolating the resulting cis isomers.[1,4] Recent syntheses are more stereoselective. A sulfone route has been developed for the synthesis of highly hindered 7-cis and 7,9-cis,cis retinal,[5] and standard methods[6] of forming carotenoids have been specifically tailored to produce other 7-cis retinals.[1,7] A [1,5]sigmatropic rearrangement of vinylallenes produces 11-cis, 11,13-cis,cis and 9,11,13-cis,cis,cis retinal.[8] Russian workers have synthesized 11-cis retinal in preparative amounts using the triphenyl-silyl protecting group.[9]

Only two retinal isomers, all-trans and 13-cis, do not form photosensitive pigments when incubated with opsin. The explanation for this behavior concerns the distance from the center of the β-ionone ring to C-15. In both of these isomers this distance in greater than that in the 11-cis isomer or any other isomer which binds to opsin. This suggests that the retinal binding site has definite longitudinal binding restrictions.[1,7d] No ring- or chain-modified analog containing the all-trans or 13-cis configuration has ever been found to form a visual pigment.‡

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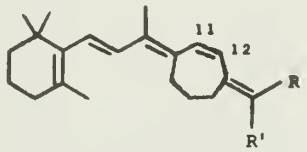
‡The protein also requires the side chain to be of a certain minimum length. Blatz, et al., synthesized a series of retinal analogues containing side chains shortened by several carbons. These did not bind with opsin.[10]

The other eleven identified stereoisomers do combine with opsin[1,7c] and the large number of artificial pigments thus possible indicate that apart from the longitudinal restrictions, the site interacting directly with the retinal side-chain is non-discriminating within a wide range of polyene geometries. Some stereoselectivity must exist, though, as the pigments obtained from isomers other than 11-cis are formed more slowly than rhodopsin.[1,7c] In some instances, these artificial pigments have also been found to be unstable in the presence of hydroxylamine and sodium borohydride,[1,7c] reagents which do not react with rhodopsin.

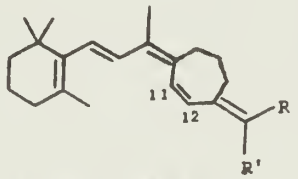
Chain modifications

Deletion and addition of methyl groups are common alterations in the retinal side chain, and these derivatives are synthesized in like fashion. The side chain of β-ionone is elongated using a directed aldol condensation and/or a Wittig or Horner-Emmons reaction with an appropriately modified phosphonium salt or phosphonate.[1,3] The products of the reactions are usually in the all-trans geometry, and they are converted to the desired cis isomers following irradiation in the appropriate solvent.[1,11]

The chain binding site is quite tolerant of extra bulk. Extra methyl groups at the 10- or 14- or 10- and 14- positions,[1] or an ethyl group at C-9[12] do not hinder pigment formation. Retinals with the 11-12 double bond locked in a cis conformation within a seven-membered ring also form pigments (2-5).[13]



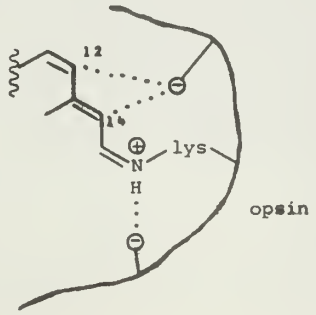
2: R=H, R'=CHO
3: R=CHO, R'=H



4: R=CHO, R'=H
5: R=H, R'=CHO

Analogues missing methyls at C-9 or C-13 or C-9 and C-13 bind to opsin.[1,10,14] These reactions are slower, however, and the corresponding photosensitive pigments are less stable than rhodopsin.[1] From these results, it has been concluded that the 9- and 13-methyl groups do interact somewhat with the opsin protein; hydrophobic or van der Waal's interactions have been suggested.[1]

One of the most significant groups of derivatives to be reported is that consisting of the 5,6-, 7,8-, 9,10- and 11,12-dihydroretinals.[1] In studying the pigments formed from these analogues and their spectroscopic properties, Nakanishi and collaborators have developed a point-charge model (6) which suggests that a negatively charged amino acid residue in the opsin is located a few Angstroms from the protonated Schiff's base linkage, and that another negative charge is present close to C-12 and C-14.[1,16]



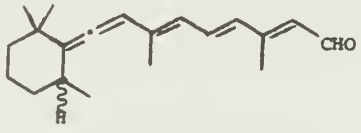
A number of chain-halogenated retinals have been successfully tested for their ability to form visual pigments. Liu has synthesized 10-, 12-, and 14-fluororetinals[1, 7d, 17] using Machleidt's procedure[18] for introducing fluorine into the vitamin A side chain. In addition, 9-bromo-9-demethyl and 13-bromo-13-demethyl retinals have been prepared and their pigment properties used as further evidence for Nakanishi's point-charge model.[1]

Ring modifications

Matsumoto, et al., demonstrated in 1975 that a pocket in the opsin molecule existed specifically for binding the β-ionone ring of retinal.[19] Much work has been carried out since then to probe the particular steric requirements of this pocket and the manner in which it interacts with the retinal ring.

The altered-ring analogues are generally synthesized using the same methodology as those with altered side chains, but with a suitably modified β-ionone ring as the precursor.[1] Very bulky moieties have been used to replace retinal's cyclohexene ring. 6,7-Didehydro-5,6-dihydroretinal (7),[20] the analogous adamantyl allenic retinal,[1] and retinals containing o-tolyl, mesityl and β-naphthyl groups[1] in place of the cyclohexene ring all form visual pigments upon incubation with opsin. As mentioned above, 7-cis retinals, whose rings are greatly twisted from the plane of the polyene chain due to steric hindrance between the 5- and 9-methyls, bind too.[1] Those derivatives containing oxygenated rings (4-oxo[21], or 5,6-epoxy[1], or 5,8-epoxy[1]) and/or rings with displaced double bonds[1,22] behave similarly. It may , therefore, be inferred that the ring-binding site of opsin is lenient in its steric and electronic requirements. But some type of binding limit is apparent, as derivatives containing meta- and para-substituted aromatic rings in place of the cyclohexene moiety do not form pigments.[7d]

Interestingly enough, the suggested hydrophobic interactions between the β-ionone ring and ring binding site are fairly critical. If a methyl group is removed from C-1 or C-5, no pigment forms.[1] Polyenes without rings do not bind to opsin either.[10,19]



7

Conclusion

From the vast variety of retinal analogues synthesized and tested for pigment formation, it would appear that, in general, the opsin site is tolerant in its steric and electronic requirements, with largely hydrophobic interactions existing between the protein and retinal. Continuing studies in this area include the use of photoaffinity[23] and isotopically[1,24] labeled retinal derivatives. These will probably be more sensitive probes in the further elucidation of the opsin-retinal binding.

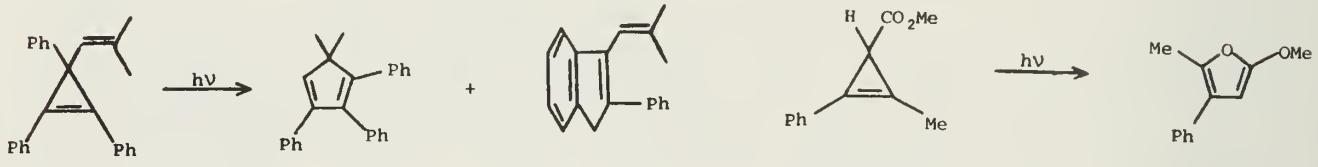
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PHOTOCHEMICAL RING-OPENING OF 3-VINYL- AND 3-ACYL-SUBSTITUTED CYCLOPROPENES

Reported by John Matthews February 23, 1984

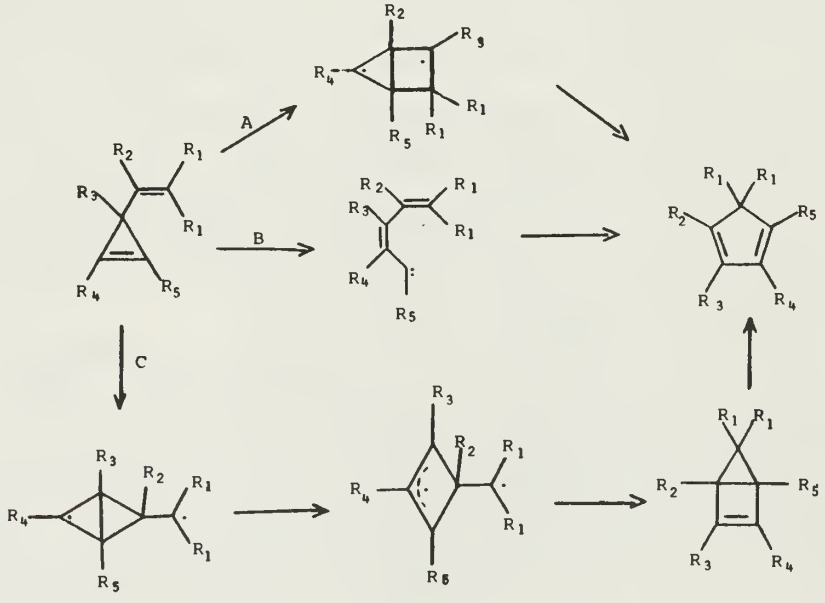
A variety of photochemical reactions has been observed with cyclopropene derivatives. One interesting feature of this photochemistry is that different reactivity is often observed for the singlet and triplet excited states.[1,2] Irradiation of 3-vinylcyclopropenes was found to give isomeric cyclopentadienes, as shown by the formation of 2 from cyclopropene 1.[3a] Indene formation (e.g., 3) was a frequent side reaction in 3-phenyl substituted compounds. In some cases other products resulted from further rearrangement of the initially formed cyclopentadiene.[3-8] Furans have been obtained in the photolysis of 3-acylcyclopropenes, as shown by the irradiation of 4 to give 5.[9a] This report will describe the scope and mechanism of cyclopentadiene and furan formation.



1 2 3 4 5

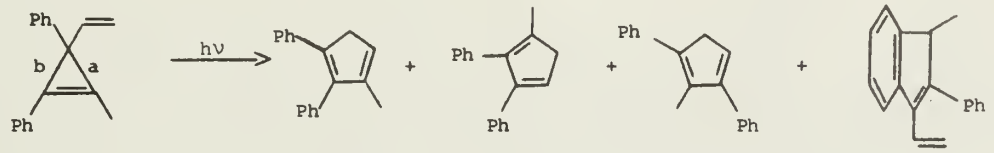
Three possible mechanisms were proposed for cyclopentadiene formation (Scheme I).[3,5] Mechanism A involves formation of a housane diradical, which fragments by a known cleavage reaction[10] to give the product. In mechanism B a vinyl carbene is formed which undergoes an electrocyclic ring closure. A third path (mechanism C) also involves a diradical intermediate.

Scheme I



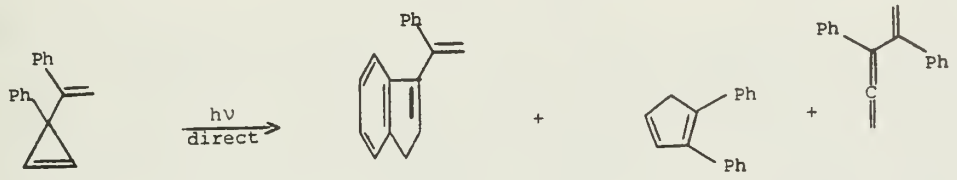
Since different product distributions were usually observed in direct and sensitized irradiations, products of direct irradiation must derive mainly from the singlet state.[3-7] Ring opening of unsymmetrically substi-

tuted cyclopropenes showed preferential cleavage of the bond adjacent to an alkyl group. For example, direct irradiation of 6 gave preferentially products from cleavage of bond a (7, 8, 10) relative to bond b (9) in a ratio of 7:1.[4]



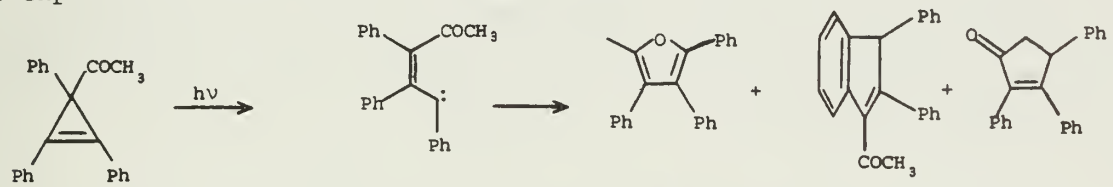
6 7 8 9 10

This trend is more consistent with mechanism A or C. The diradical resulting from cleavage of bond a would be stabilized by the adjacent phenyl group. However, some products, such as allene 14, can be explained more easily by mechanism B.[7] The possibility of the reaction proceeding by some intermediate pathway cannot be ruled out.[6,7] On the other hand, of the three proposed mechanisms, only C can account for some aspects of the corresponding triplet photochemistry.[8]



11 12 13 14

The involvement of a vinyl carbene intermediate has been suggested in the photochemistry of 3-acylcyclopropenes.[9] The formation of ketone 18 can be explained in terms of an insertion into a methyl C-H bond.[9b]



15 16 17 18

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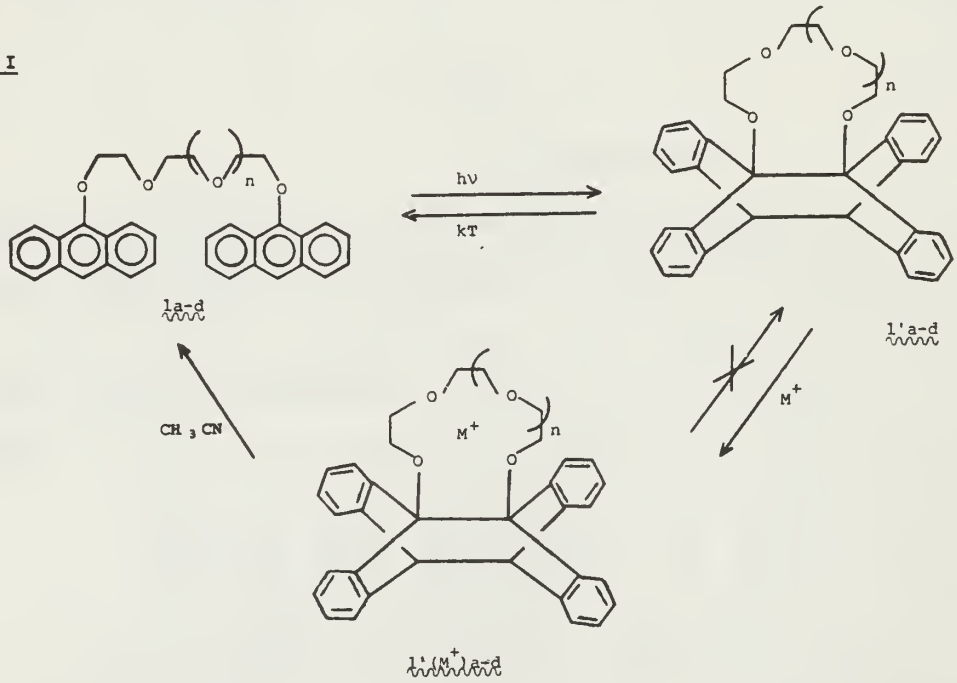
PHOTORESPONSIVE CROWN ETHERS

Reported by Yu-Zhuo Li February 27, 1984

Photoregulated processes, such as photosynthesis, vision, phototropism, and photomotion, are important in nature.[1] As a first step towards mimicking natural phenomena, several systems have been designed and studied in which a photoantenna group, used to capture a photon, is combined with a functional group to mediate some subsequent event, such as transportation of ions across a membrane. In order for a chemical segment to function as a photoantenna, the following requirements[2] must be met: 1) the photoinduced geometrical change must be reversible and reproducible, 2) the geometrical change must provide a large conformational change in the functional group, and 3) the quantum yield of the photoinduced reaction must be high. In practice, the isomerization of azobenzenes or spiropyrans[3] and the formation of anthracene dimers from dianthrylalkanes have been used at various times to regulate the function of metal ligands, β and γ-cyclodextrines,[4] artificial membranes,[5] and polypeptides,[6] and the properties of polymers.[7]

Considerable interest has been focused on the function of crown ethers as ion transport carriers across lipid bilayer or artificial membranes.[8] Monensin, a naturally occurring mobile carrier, undergoes a conformational change between its cyclic and non-cyclic forms that facilitates first ion complexation and later ion release.[9] Researchers have attempted to duplicate monensin's behavior by designing photoactivated ring-closing crown ethers. The first photogenerated "cation locked" crown ether, 1a, was reported by Desvergne, et al.[10] This compound, 1a, undergoes photoinduced cyclomerization to form the free cyclomer, which is relatively unstable ($t_{1/2}$= 3 min. at 30 °C). However, in the presence of a cation, such as K^+, Na^+ or Li^+, the cyclomer forms a cation locked complex which is stable up to 206-210 °C and then decomposes with charring. The studies,[11] which involved extension of the polyoxaalkane chain and insertion of methylene groups into the crown show that the instability of 1a is caused by a strong repulsion between oxygen atoms in the crown (Scheme I).

Scheme I

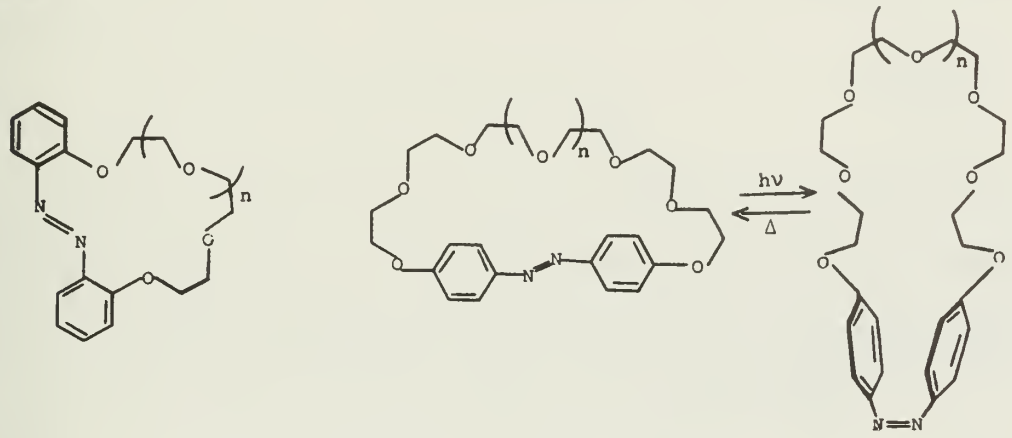


1a: n = 1
b: n = 2
c: n = 3
d: n = 4

$M^+ = Li^+, Na^+, K^+$

Shiga and his coworkers[12] started the study of a new family of crown ethers with a chromophoric azobenzene group directly incorporated into the crown skeleton. The interconversion of cis and trans forms is easily followed by observing the spectral change in the UV region. The result suggests that the photo-isomerized forms of 6 and 7 have less binding ability to alkali metal ions than their trans forms do. A modified form of this system, 8a, actually is the first crown ether designed which exhibits an all-or-nothing photoresponsive property (Scheme II).[13] The results indicate that the cis form of 8 with n + 6 oxygens in the crown behave like a normal crown ether with n + 4 oxygens (and no azobenzene group).' In contrast, the trans form of 8, the thermally stable form, has no binding ability at all.

Scheme II



6, n = 1
7, n = 2

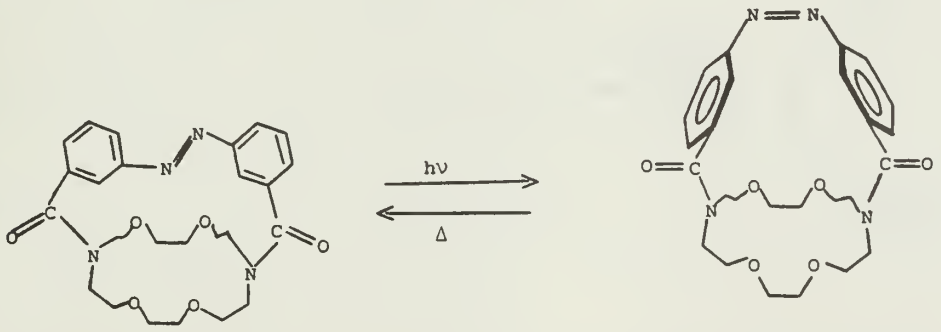
trans - 8a-c

cis - 8a-c

8a, n = 1
b, n = 2
c, n = 3

It has been well established that the metal ion affinity of crown ethers depends upon the size of the crown.[14] Studies on a series of azobenzene-bridged crown ethers show that the binding ability of the ether depends on the photoisomer present;[15] i.e., the range of the extractability of trans-9 is shifted from K^+, Na^+, Li^+ to Rb^+, K^+, Na^+ by exposure to light. This result is rationalised in terms of a photoinduced expansion of the crown size (Scheme III).[16,17]

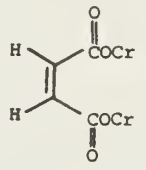
Scheme III



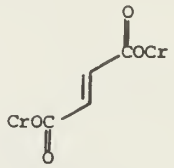
trans - 9

cis - 9

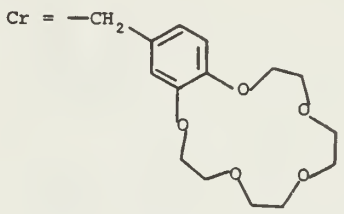
Based on the host-guest relationship between macrocyclic polyethers and metal ions, it is believed that alkali cations which exactly fit the cavity of the crown ether form 1:1 cation/crown complexes, while those with larger ionic radii form 1:2 cation/crown complexes.[8] This view was well demonstrated by a study using bis(crown ether)s. For example, the maleate derivative of benzo-15-crown-5 extracts K^+ ions from the aqueous solution into the organic phase 14 times more efficiently than the fumarate derivative does. This selectivity is caused by the formation of an intramolecular complex with the cation sandwiched between the two crowns only in the cis form.[18] When C=C double bonds are replaced by N=N double bonds, the cis-trans isomerization of an azobenzene group can cause the bis(crown ether) to undergo a butterfly-like motion which, in turn, stabilizes or destabilized the complexes (Scheme IV).[19] Further studies show that the size of the crown, the rigidity and the symmetry of the wings, and the nature of the counterion are also very important factors which affect the rate of ion transport.[20,21,22]



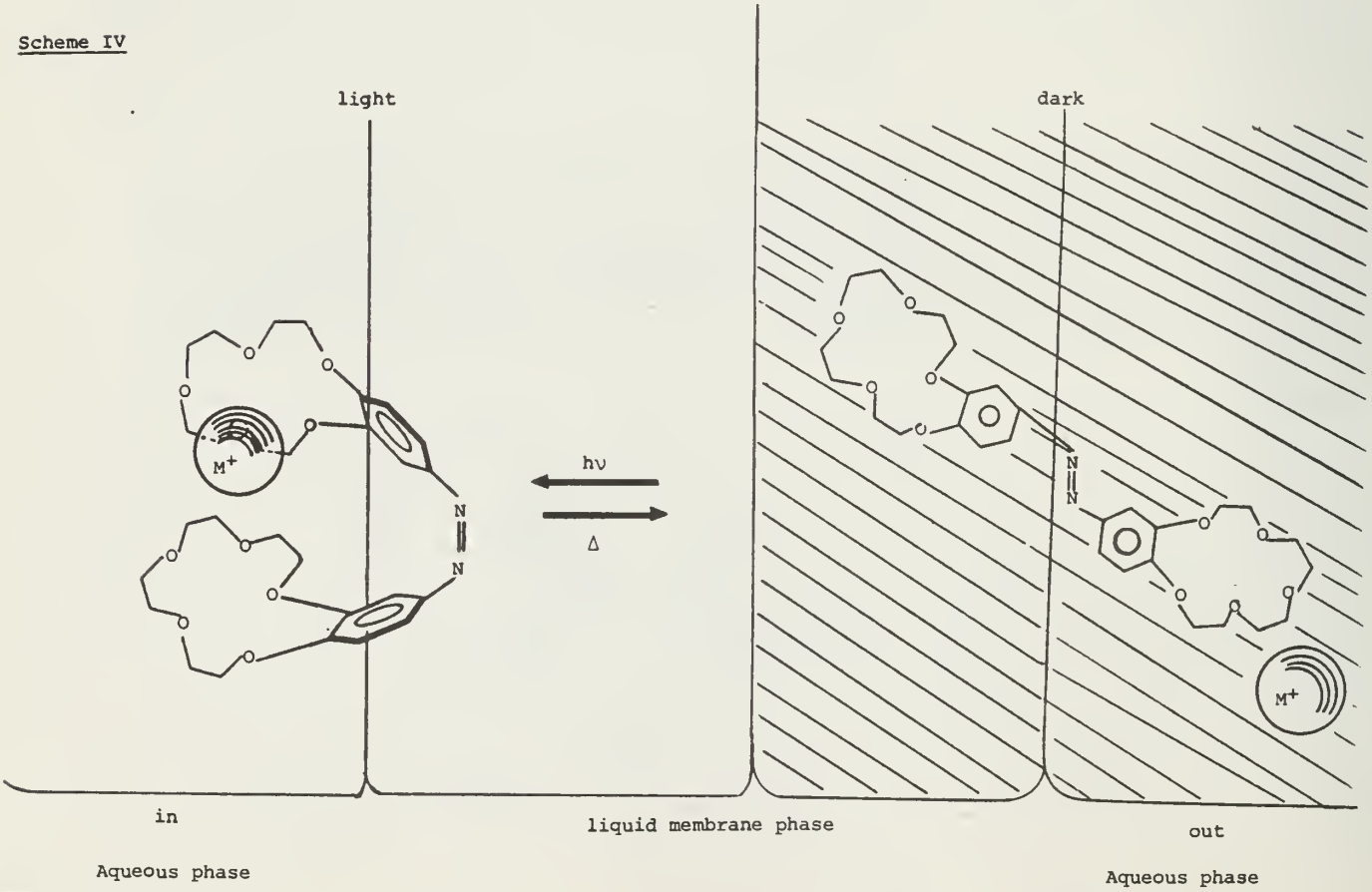
Maleate derivative



fumarate derivative

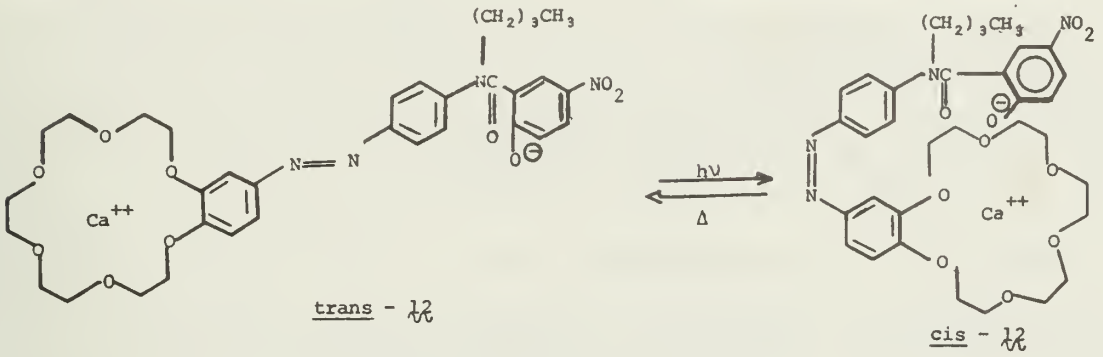


Scheme IV



Upon irradiation with UV light, the ionophore 12, in which the crown ether ring bears an anionic phenoxide arm, isomerizes to the cis form which provides a more comfortable cavity for Ca^{++} than its trans form does. Therefore, the transport of the Ca^{++} ion is efficiently mediated with the ionophore 12 (Scheme V).[23]

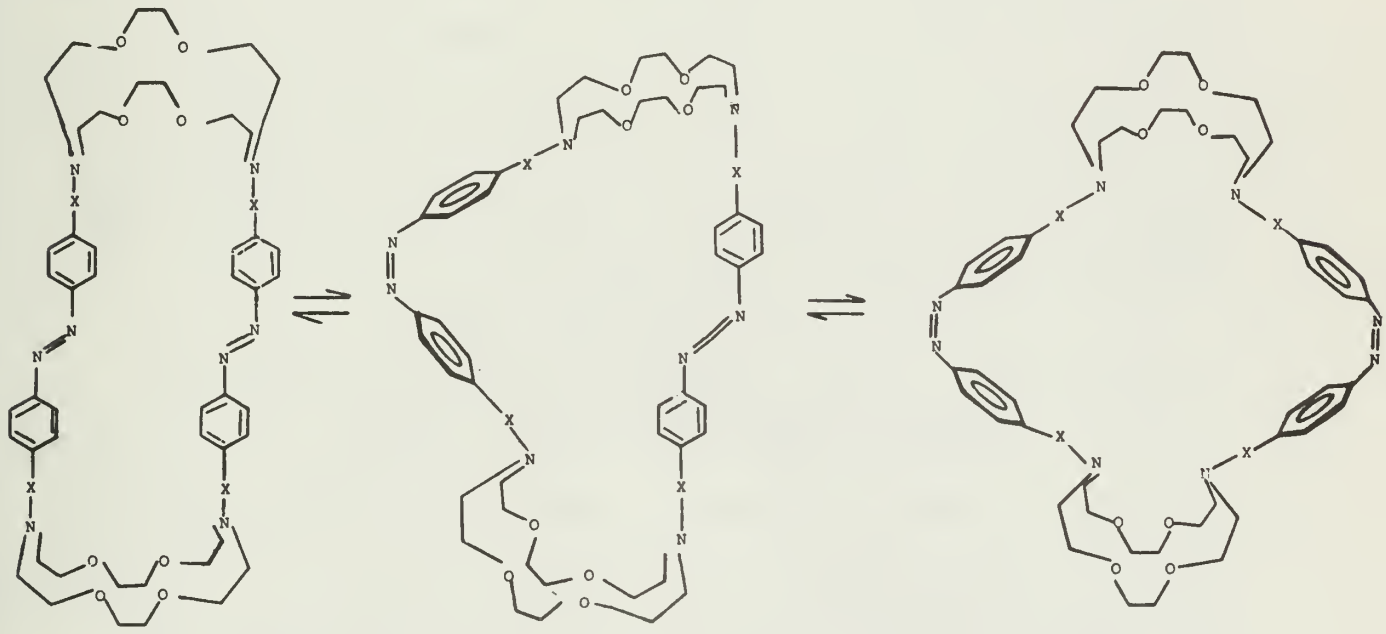
Scheme V



trans - 12 cis - 12

Cylindrical ionophores, with two crown ether segments linked by two or more pillars can bind more than one metal ion and selectively bind some alkanediammonium ions.[24] The selectivity is controlled by the size of the crown and the pillar length. Since the distance between the 4- and 4'-positions of trans-azobenzene (9.0 Å) is different from that of the cis form (5.0 Å), the isomerization of the azobenzene segment can change the cavity size and influence the binding selectivity (Scheme VI).[25,26]

Scheme VI



trans, trans - 13a,b trans, cis - 13a,b cis, cis - 13a,b

13a: X = CO
13b: X = OCH_2CO

In addition to the systems containing only a photoantenna group and a crown ether, systems have also been designed in which the photoantenna and crown ether are incorporated into polymers. Since the surface of the polymer beads can be considered to be one side of a membrane, the application of the polymer-supported photoresponsive crown ethers would be attractive for use as artificial membranes.[27]

For the future, chemical substances which exhibit photoresponsive changes are candidates not only for use as chemical condensers in the storage of light energy but also for use as mediators in the translation of light energy into chemical function. Studies of photoresponsive crown ethers may help lead to the development of an "on-off" switch for the control of chemical functions.

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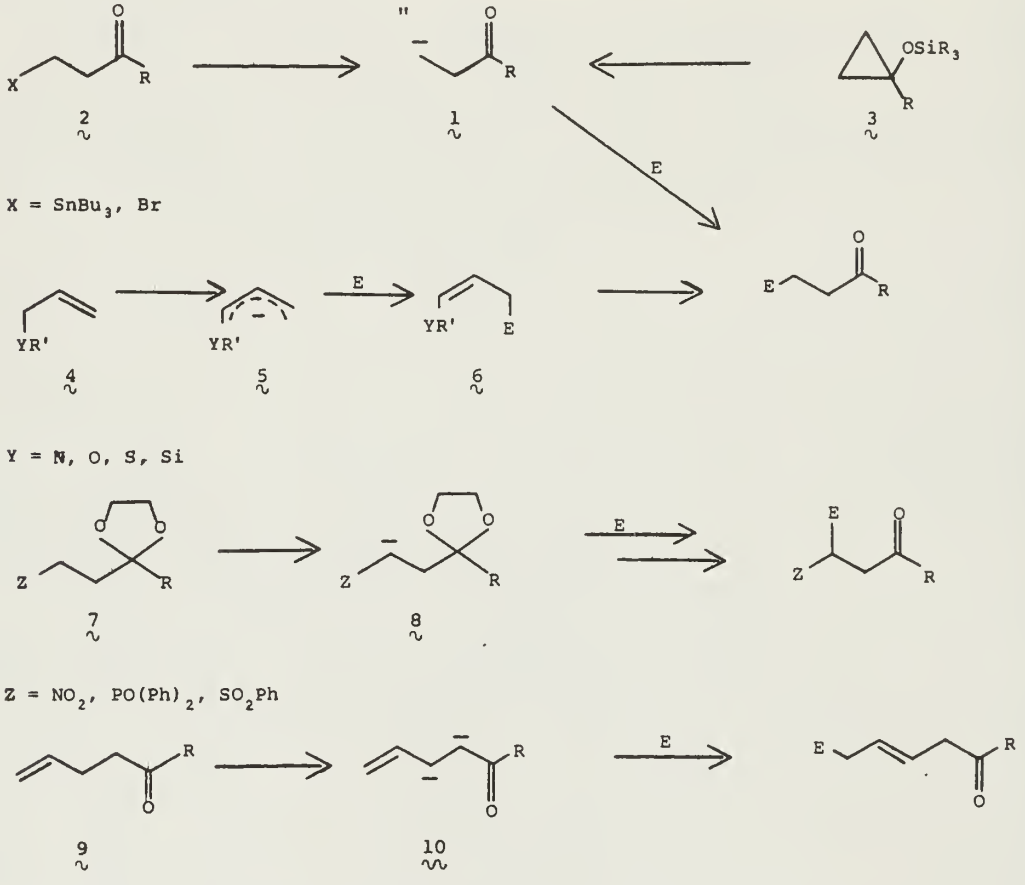
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THE GENERATION OF FORMAL HOMOENOLATES VIA AMIDE-DIRECTED METALATION

Reported by James E. Hunter March 1, 1984

The development and understanding of new methods for conversion of carbon hydrogen bonds to carbon carbon bonds is of considerable importance to organic chemists. Synthetically, umpolung reactions,[1] which complement many of the classical synthetic methods, are particularly desirable. It comes as no surprise, then, that methods which impart nucleophilic character at carbon centers β or δ to a carbonyl moiety have been of recent interest.[2]

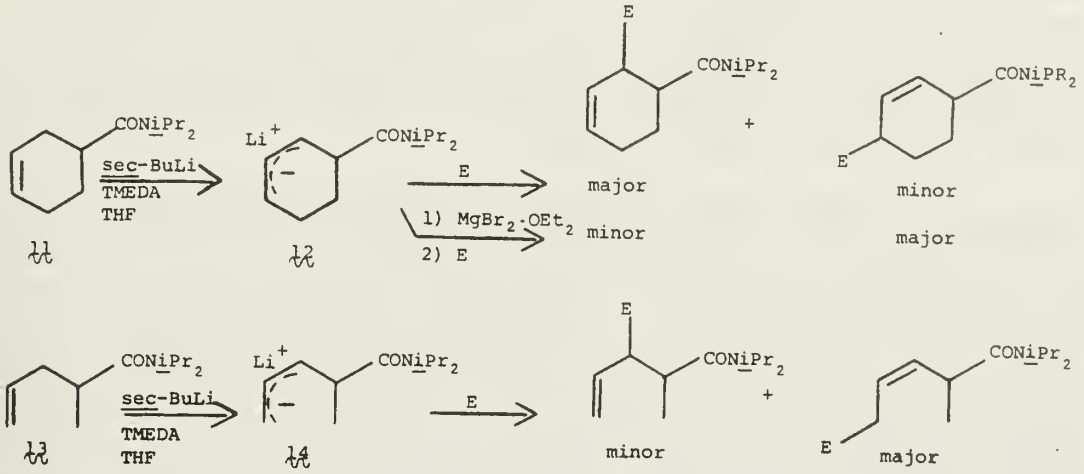
Preparations of formal homoenolate 1 can be achieved by halogen-metal[3] or lithio-tin[4] exchange of appropriate precursors, 2, as well as by the opening of cyclopropyl silyl ethers, 3, with titanium(IV) chloride.[5] Allyl anions with terminally bonded heteroatoms, 5, are used extensively as homoenolate equivalents. The heterosubstituted olefins, 6, from γ-addition of an electrophile may be unmasked to the corresponding carbonyl compound.[2] Compounds with anion stabilizing groups on a carbon β to a masked ketone, 7, are used as well.[2] Anions can also be formed β to ketones as the dianions of γ,δ-unsaturated compounds, 9.[6] In this case, however, electrophiles are incorporated δ to the carbonyl.



Amides have proven to be powerful directing groups. The N,N-diisopropylcarboxamide group, in particular, directs ortho metalation in aromatic amides[7] and β'-deprotonation of α,β-unsaturated alphatic amides.[8] We have recently found the directing ability of this amide may be extended to γ,δ-unsaturated systems in which the β-proton is preferentially abstracted over the potentially more acidic α-proton.[9]

Metalation is achieved by treating N,N-diisopropylcyclohex-3-enecarboxamide 11, or N,N-diisopropyl-2-methylpent-4-enecarboxamide, 13, with sec-butyllithium/tetramethylethylenediamine in tetrahydrofuran. Both anions react with a variety of electrophiles in good to moderate yields with β-addition products generally

obtained as the major products in the cyclic system and δ-substituted β,γ-unsaturated amides of cis geometry obtained from the acyclic amides. The regioselectivity of electrophilic substitution is altered in both cases by the addition of magnesium bromide etherate to the allyllithium anion. Addition at the δ position of allyl anion, 12, in a highly stereoselective manner predominates in that case. It was established by alternative synthesis that alkyl halides add trans to the carboxamide moiety.



The course of lithiation is attributed to an amide-base complex, which brings the alkyllithium into close proximity to the β-protons. Such complexes have been observed spectroscopically in the formation of a dipole-stabilized carbanion in the α'-lithiation of N,N-dimethyl-2,4,6-triisopropylbenzamide with sec-butyllithium.[10] The change in regiochemistry in alkylation is attributed to reactivity differences derived from allyl metal chelation. Allylithium is known to have a structure with the lithium disposed symmetrically about the π system.[11] Electrophilic addition may occur at either the β or δ positions. Allylmagnesium bromide, however, is a system with the magnesium rapidly oscillating its bonding between the two terminal carbons.[11] Presumably, reaction takes place via an S_E2' pathway discussed by Felkin.[12]

In summary, γ,δ-unsaturated amides 11 and 13 may be deprotonated to give formal homoenolates. The anions can be trapped with electrophiles with some degree of regio- and stereospecificity, which may be altered by changing the chelating metal. The deprotonation reaction is unique, in that the proximity effect of complexation dominates over the resonance and inductive effects of the carbonyl in directing metalation.

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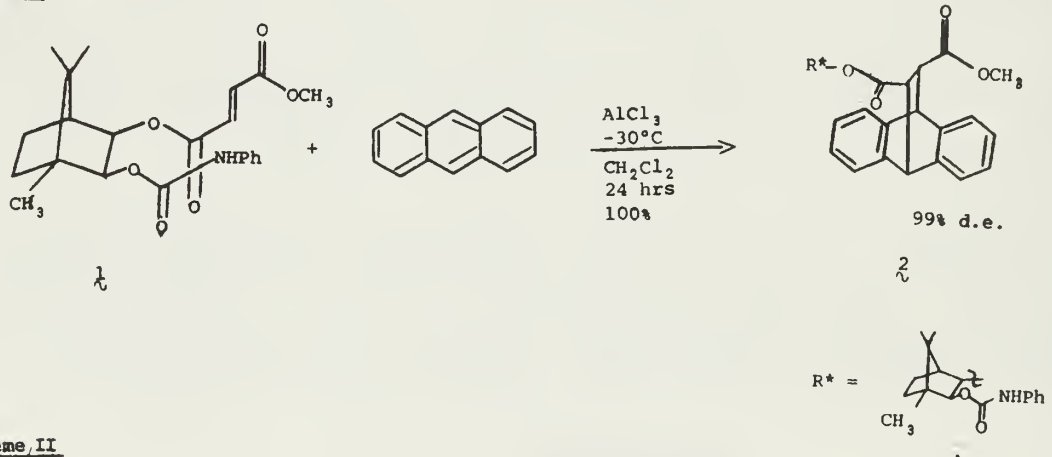
ASYMMETRIC DIELS-ALDER REACTIONS

Reported by Jeffrey Sternberg March 5, 1984

Since its discovery in 1928, the Diels-Alder reaction has been one of the most powerful tools in synthetic organic chemistry.[1] The simultaneous creation of four contiguous chiral centers with predictable relative stereochemical control has made the reaction extremely valuable in countless chiral syntheses. However, additional stereochemical control by the introduction of a chiral directing agent was not actively pursued until 1963. In recent years this idea has received considerable attention, using various methodologies to afford a high degree of asymmetric induction. A survey of the endeavors in this field is the topic of this seminar.[2]

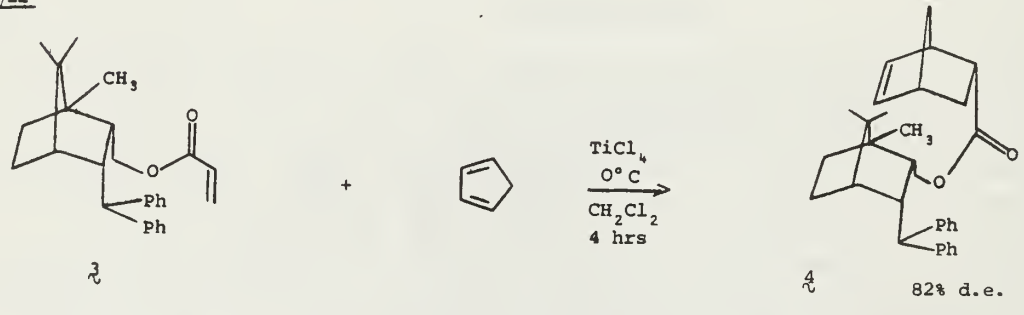
Chiral Dienophiles. Prior to 1981, few examples of efficient asymmetric induction utilizing the Diels-Alder reaction existed.[3] Since then, a number of chiral acrylate dienophiles have been developed which exhibit dramatically improved diastereomeric selectivity. For example, Schmierer[4] observed high asymmetric induction in the Lewis acid-catalyzed Diels-Alder reaction of cis/exo fumarate 1 with anthracene (Scheme I). The carbamate functionality effectively hindered diene approach from the Re-face of the enoate, thereby leading to a 99% diastereomeric excess of 2.[4] Oppolzer[5] investigated the Diels-Alder reaction of cyclopentadiene with cis/endo camphor-derived acrylates such as 3 and found that they too yield high asymmetric induction of the anticipated cycloadducts such as 4 (Scheme II). Other acrylates derived from a series of optically active monoterpenes behaved similarly upon treatment with cyclopentadiene.[5]

Scheme I



1 2

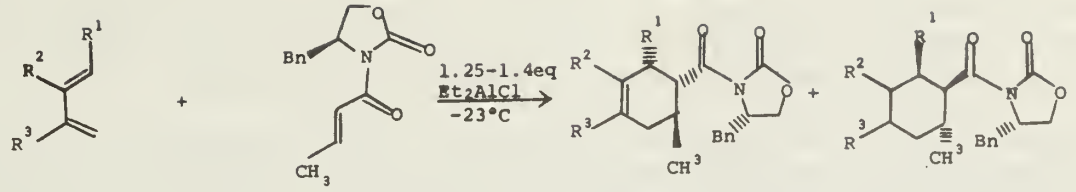
Scheme II



3 4

Only very recently have asymmetric Diels-Alder reactions utilizing chiral dienophiles other than acrylate esters been studied. Evans[6] introduced chiral crotonate imides, such as 6, which react with a variety of dienes to afford high asymmetric induction in the presence of a Lewis acid (Scheme III, Table I). The benzyl-substituted N-acyl oxazolidone 6 was synthesized in three steps from (L)-phenylalanine.[6a] Other chiral crotonates and acrylates were synthesized in an analogous fashion and treated with dienes to give comparable stereoselectivities.[6]

Scheme III



5a-c 6 7a 7b

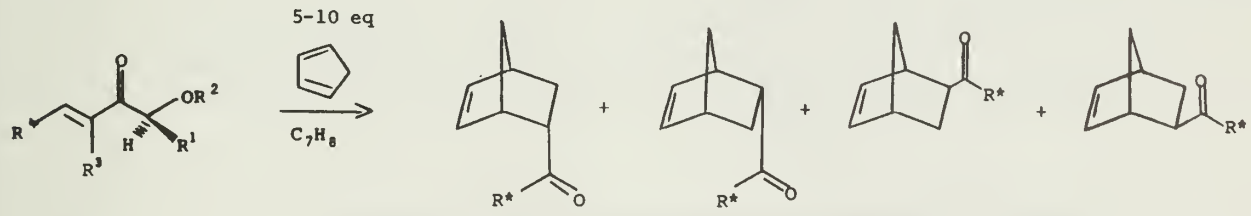
Table I Diels-Alder Reactions of Substituted Butadienes and N-Crotonyl Oxazolidones

	R^1	R^2	R^3	Time (hrs)	7a/7b
5a	H	H	Me	5.5	93/7
5b	H	Me	Me	5.5	92/8
5c	Me	H	H	7	93/7

The Diels-Alder reactions of 6 with a series of acyclic dienes 5a-c exhibited excellent diastereoselectivities, as shown in Table I.[10a] In each instance, the dienophile reacted within a few hours at relatively low temperatures to give an excellent yield of endo isomer 7a or 7b. At most only a few percent of the exo isomer was isolated. The superb diastereoselectivities observed support a transition state involving two-point contact between the Lewis acid and both carbonyl oxygens.[6a] This dichelated complex was thereby frozen in a rigid conformation with an unambiguous topological bias.[6a]

Recently, Masamune, et al.,[7] developed a novel family of chiral dieneophiles which achieved excellent diastereoselectivity in the absence of Lewis acid catalysis (Scheme IV, Table II).[7] The vinyl ketones 8a-8c enjoy attachment of the chiral auxiliary one atom closer to the olefin than the chiral esters employed previously.[2-5] Hydrogenation of (S)-mandelic acid[7b] followed by treatment with vinyllithium yielded ketol 8a.[7a] Addition of tert-butyldimethylsilyl triflate afforded 8b.[7a] Conversion of (S)-2-hydroxy-3,3-dimethylbutanoic acid to 8c proceeded in the same manner.

Scheme IV



8a-c 9a 9b 9c 9d

Table II Diels-Alder Reactions of Chiral Vinyl Ketones with Cyclopentadiene

	R^1	R^2	R^3	R^4	T° (hrs)	9a:9b	9c:9d	(9a+9b)/(9c+9d)	total yield
8a	C_6H_{11}	H	H	H[a]	-55°(17b)	28:1	7:1	6/1	—
8b	C_6H_{11}	Si-t-BuMe$_2$	H	H	r.t.(18)	3:2	3:2	3/1	—
8c	t-Bu	H	H	H	-20°(24)	100:1	b	8/1	90%

[a] solvent - CH_2Cl_2

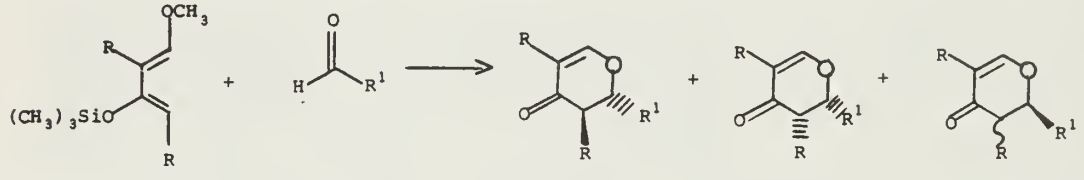
[b] none of the exo isomer 9d was detected by 250-MHz-NMR

From the results summarized in Table II, Masamune[7a,c] postulated that ketols such as 8a and 8c favor a cisoid conformation with the hydroxyl proton chelating with the carbonyl. This intramolecular chelation is unavailable to the silyl ether 8b, thereby lowering its diastereoselectivity.

Asymmetric cyclocondensation reactions of chiral aldehydes with siloxydienes were also investigated (Scheme V, Table III).[9] According to Danishefsky[9] the mechanism of the reaction depends on the Lewis acid catalyst used. When boron trifluoride etherate was used the reaction proceeded through an aldol-like mechanism while zinc chloride catalyzed a hetero-Diels-Alder process.[9d] Furthermore, he argued that the cycloaddition proceeded through a transition state in which the aldehyde substituent was endo, thereby allowing the bulky, antiperiplanar-bound Lewis acid to be away from the diene.[9a]

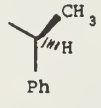
When the aldehyde bore a chiral auxiliary then the direction of approach was governed by Cram's rule,[9,10] as illustrated in the cyclocondensation of siloxydiene 10 with aldehyde 11a (Table III). When magnesium bromide was employed as a catalyst only the exo-anti-Cram‡ product 12a or 12b was isolated upon treatment of the chiral aldehyde 11b with the siloxydiene 10a or 10b, respectively.[9b] To explain this , Danishefsky envisioned a transition state in which the magnesium chelated with both the carbonyl and ether oxygens to form a bulky bidentate complex.[9a] The aldehyde substituent in this case preferred an exo orientation, but diene approach still occurred from the less hindered side.

Scheme V



10a-b 11a-b 12a 12b 12c

a: R - CH_3 a: R^1 =



b: R = H b: R^1 =

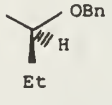


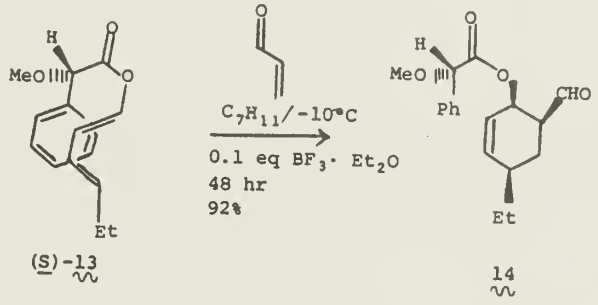
Table III Siloxydiene Cyclocondensations with Chiral Aldehydes

diene	aldehyde	conditions	12a:12b	12b:12c
10a	11a	1eq. $ZnCl_2$ THF/r.t.	0:1	—
10a	11b	$MgBr_2$/THF	1:0	—
10b	11b	$MgBr_2$/THF	—	1:0

‡ "anti-Cram" implies attack from the more hindered side when the aldehyde assumes the stable, Cram[10] conformation.

Chiral Dienes. Diels-Alder reactions in which the chiral auxiliary is borne on the diene have also been studied; however, the degree of asymmetric induction achieved remains slightly lower. In the synthesis of (+)-ibogamine, Trost[11a] established the correct absolute stereochemistry at three of the four chiral centers in the Diels-Alder reaction of diene (S)-13 with acrolein (Scheme VI). He proposed that the 60% excess of cycloadduct 14 arose from the phenyl ring shielding one side of the diene from attack.[11] In this so called "π-stacking model,"[11] the diene shared the same half-space as the smaller substituent (H opposed the OMe in (S)-13) in order to minimize steric congestion (Scheme VI). Other examples in the literature lend support to Trost's model.[11b]

Scheme VI



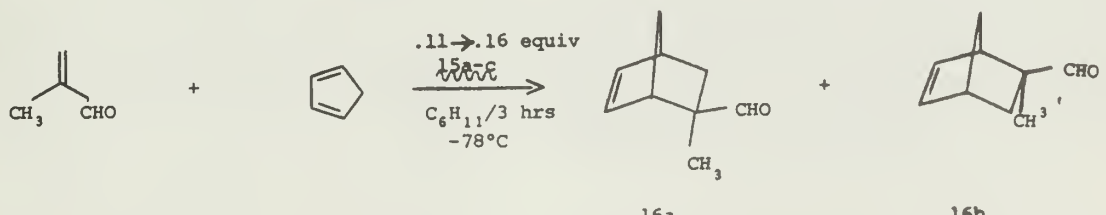
(S)-13 14

Chiral Lewis Acids.[13] Chiral Lewis acids represent the potentially most efficient method of controlling asymmetric induction in the Diels-Alder process since the chiral agent is required in only catalytic amounts and can be removed and regenerated without further chemical transformations.[6a] Unfortunately, this avenue of stereochemical control has proved difficult due to the distance of the chiral agent from the reaction center and the conformational mobility of the systems involved.

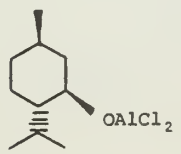
The most recent investigation in the area used $Eu(hfc)_3$ and diene 17c (Table V).[12] The origin of the asymmetric induction in this cyclocondensation reaction has not been resolved.

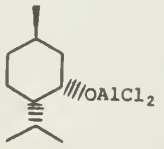
Earlier work by Koga[14] using chiral alkoxyaluminumdichloride Lewis acids 15a-c to catalyze Diels-Alder reactions met with limited success. Results of their reactions with cyclopentadiene and 2-methylpropenal are outlined in Scheme VII and Table IV.[14] None of the catalysts 15a-c imparted high enantioselectivities when methyl acrylate or acrolin was used as the dienophile.[14] A transition state was not suggested by Koga, and the major product could not be predicted simply from the configuration at the closest chiral center to the aluminum.

Scheme VII



16a 16b

15a 

15b 

15c 

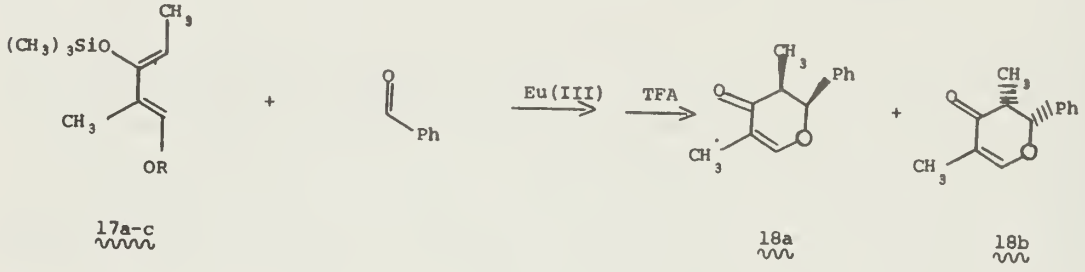
Table IV Effect of Chiral Lewis Acids on the Diels-Alder Reaction

Lewis Acid	yield	16a:16b
15a	69%	14:86
15b	72%	83:17
15c	84%	37:63

Double Asymmetric Induction.[7a] In all of the cases mentioned above, only one of the Diels-Alder reactants bears a chiral auxiliary; however, one can achieve better stereoselectivities if two chiral reagents are involved.[7c]

For example, the aldehyde-siloxydiene cyclocondensation reactions pioneered by Danishefsky have been extended to the use of chiral dienes along with chiral catalysts (Scheme VIII, Table V).[12] When $Eu(fod)_3$ was added as a catalyst neither the (+)- nor (-)-menthyl substituted diene 17a nor 17b combined with benzaldehyde to give any significant enantioselectivity.[12b] When the chiral shift reagent $Eu(hfc)_3$ was used as a catalyst little enantioselectivity was observed for diene 17a, but the enantioselectivity increased dramatically when diene 17b was used. A transition state reflecting these observations has not been proposed.[12b]

Scheme VIII



17a-c 18a 18b

Table V Double Asymmetric Induction in Siloxydiene-Aldyhyde Condensations.

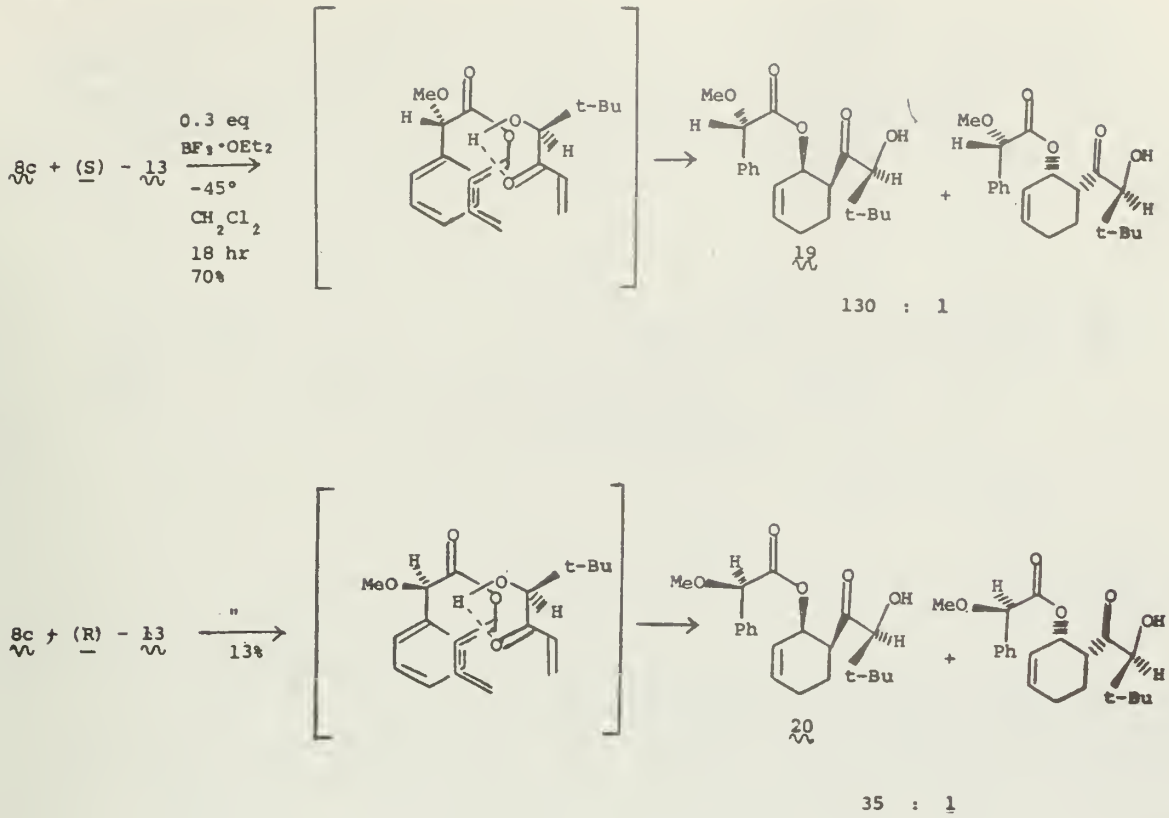
	R	Eu(III)	18a:18b
17a	(+)-menthyl	$Eu(fod)_3$[a]	49:51
17b	(-)-menthyl	"	51:49
17a	(+)-menthyl	$Eu(hfc)_3$[b]	49:51
17b	(-)-menthyl	"	13:87
17c	methyl	"	26:75

[a] $Eu(fod)_3$ = tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium

[b] $Eu(hfc)_3$ = tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium

Masamune[7c] observed diastereoselectivities as high as 130:1 when the chiral diene (S)-13 combined with the chiral ketol 8c (Scheme IX).[7c] The major cycloadduct 19 was visualized arising from a transition state in which the diene assumed the π-stacked conformation,[11] the dienophile underwent internal chelation,[7c] and the direction of approach minimized steric crowding between reactants.[7c,11] In this example, the diene and dienophile were regarded as matched chiral partners.[7c,8]

Scheme IX



In the Diels-Alder reaction of (R)-13 with the same dienophile 8c the reactants were mismatched and, therefore, gave rise to only a 35:1 diastereomeric ratio (Scheme IX).[7c] The configuration of the major product 20 reflected the fact that the dienophile, rather than the diene, exerted the stronger directing ability.[7c]

Intramolecular Asymmetric Diels-Alder Reactions. The value of an intramolecular asymmetric Diels-Alder reaction has been recognized in recent years due to its ability to form a variety of polycyclic systems with significant diastereomeric control.[15-17] The chiral oxazolidones introduced by Evans[6] have been applied to the synthesis of trans-[4.3.0] bicyclononene and [4.4.0] bicyclodecene systems (Scheme X, Table VI).[6a] Never was more than 1% of the exo isomer isolated, and the major endo product resulted from the sterically less encumbered approach to the bidentate complex.[6]

Scheme X

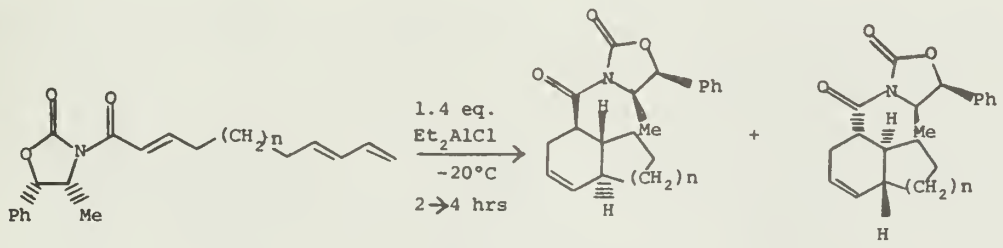
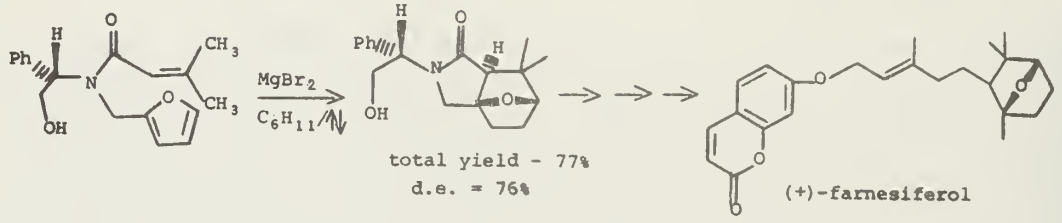


Table VI

n	yield of 21a	21a:21b
1	55%	83:17
2	67%	90:10

In the total synthesis of (+)-farnesiferol, Mukaiyama[16] established the absolute configuration of all three chiral centers in one step (Scheme XI). Intramolecular cyclization of 22 gave an 88:12 mixture of diastereomers in 77% yield.[16] The transition state leading to 23 minimized the steric repulsion between the methylene protons adjacent to the furan nucleus and the phenyl ring.[16]

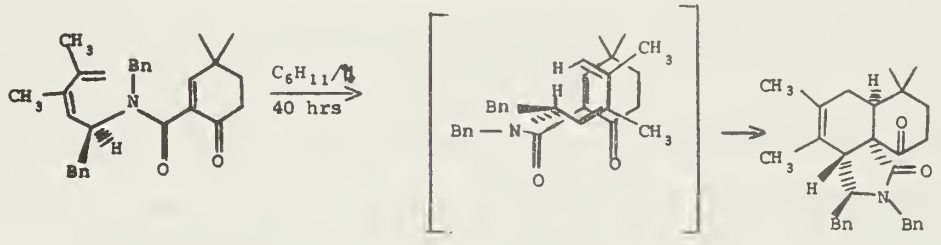
Scheme XI



22 23

Fuchs and co-workers[17] examined the use of an intramolecular asymmetric Diels-Alder reaction in a model study for cytochalasin C (Scheme XII). The intramolecular cyclization of 24 produced, in 95% yield, the single cycloadduct 25 possessing the anticipated stereochemistry of the lactam ring.[17] A transition state geometry consistent with the observed stereochemical outcome is illustrated in Scheme XII.

Scheme XII



24 25

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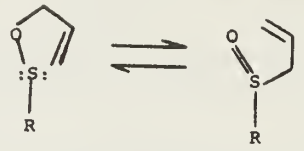
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RECENT SYNTHETIC APPLICATIONS OF THE ALLYLIC SULFOXIDE-SULFENATE [2,3] SIGMATROPIC REARRANGEMENT

Reported by Ernest B. Clark March 8, 1984

The facile thermal racemization of allylic chiral sulfoxides led Mislow and co-workers to propose in 1968 the operation of a reversible [2,3] sigmatropic rearrangement between allylic sulfoxides and their isomeric sulfenates (Scheme I).[1] The relative ease with which allylic structures can be given sulfur functionality and the transformations available from either side of the Scheme I equilibrium make the rearrangement a powerful tool for the synthetic chemist faced with the manipulation of allylic structures.

Scheme I



The characteristics of the rearrangement are well established.[2] The equilibrium lies well over on the sulfoxide side; the rearrangement is concerted and stereospecific; and, with proper choice of substituents, chirality transfer can occur across the equilibrium.[3-4]

By far the most common synthetic application of the rearrangement is to position an allylic alcohol group correctly. A typical procedure for this would be to treat an olefin with phenylsulfenyl chloride to form an allylic sulfide, oxidize to the sulfoxide, and trap the isomeric sulfenate ester with a thiophile to produce an allylic alcohol, as done by Kurozumi and co-workers in their stereocontrolled synthesis of prostaglandin analogs.[5] Similar allylic sulfide → sulfoxide → rearranged alcohol routes have been followed in the synthesis of α-methylenebutyrolactones,[6] withanolides,[7] and cembranolides.[8] Several convergent syntheses have followed a similar route after the alkylation of a metalated allylic sulfide.[9-14] Guittet and Julia have formed sesquiterpenes by treating epoxides with lithiated allylic sulfoxides; after addition the system is free to rearrange to the desired product.[15] The procedure of Mimura and Nakai for transposing enone functionality by one carbon uses a sulfenate rearrangement in its direction-determining step.[16]

Several other synthetic transformations involving the allylic sulfoxide sulfenate rearrangement have been investigated. Reich and Wollowitz have transformed allylic alcohols into 1,3-dienes by forming their sulfenyl esters, followed by thermal syn elimination of sulfenic acid from the rearranged sulfoxides.[17] Grieco has isomerized Z-allylic alcohols by forming their sulfenate esters. After immediate rearrangement to the sulfoxides, E-allylic sulfenates are formed and trapped far more readily than the starting Z-isomers.[18-19] Propargylic alcohols have been sulfenylated and rearranged to butadienes,[20-21] drimatrienes,[22] and vinylallene or vinylacetylene sulfoxides.[23] Three syntheses of cephem and related ring systems invoke the sulfoxide-sulfenate rearrangement,[24-26] and it has also been used to form 14α-methyl-19-norsteroids[27] and 5-deoxyleukotriene D.[28]

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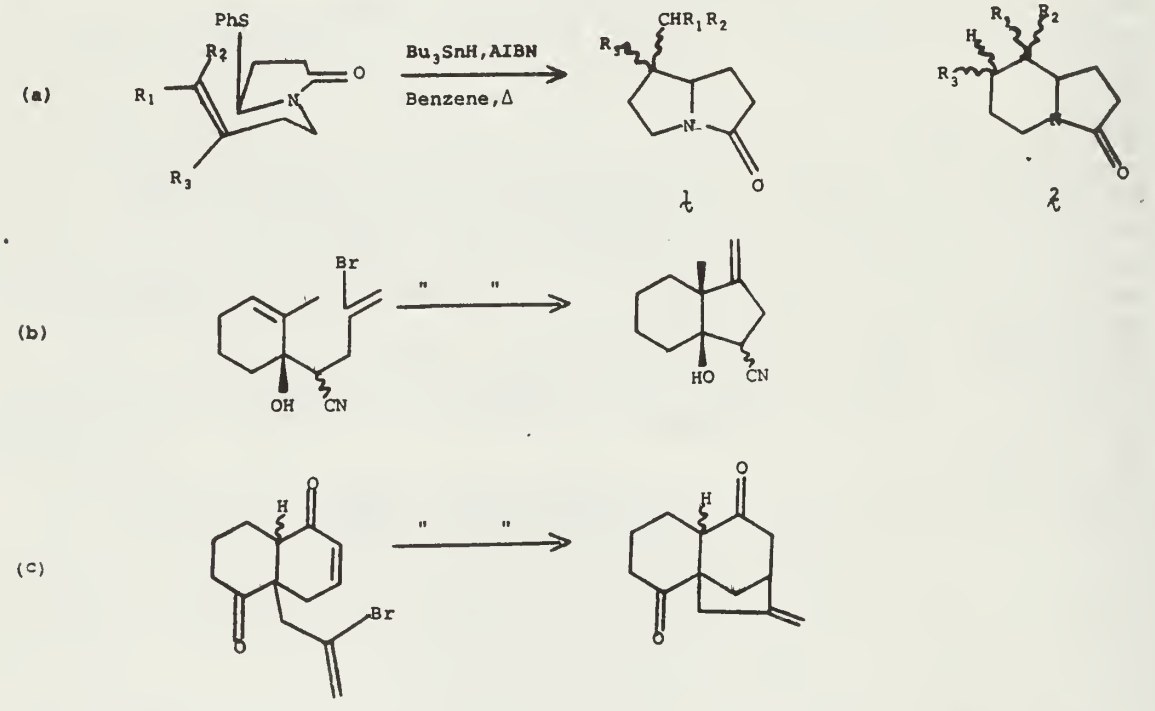
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FORMATION OF BICYCLIC SYSTEMS BY CARBON RADICAL CYCLIZATIONS TO MULTIPLE BONDS

Reported by Jeff A. Zablocki March 19, 1984

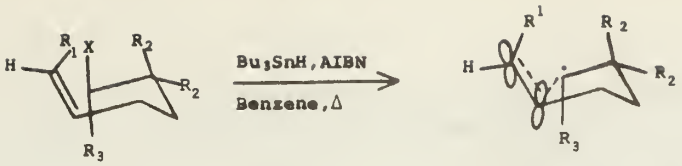
The recent ability to control regiochemistry and stereochemistry in radical cyclizations to form functionalized bicyclic systems should lead to an increased use of radical cyclizations in the synthesis of natural products.[1] Hart and co-workers were able to control the regiochemical course of α-acylamino radical cyclization so as to give pyrrolizidinones, 1, indolizidinones, 2, by varying the substitution on the double bond (Scheme Ia) or by using trimethylsilyl alkynes.[2] The α-acylamino radical cyclization could be useful in the synthesis of pyrrolizidines, indolizidines, and other alkaloids (Gephrotoxin or β-lactam antibiotics[3]). Stork and co-workers have used free radical cyclization of bromoacetals in the construction of bicyclic acetals and lactones.[4] In addition, his group has used the vinyl radical (generated from a vinyl halide or in situ by the addition of another radical to a triple bond) to form various bicyclic systems regiospecifically and stereospecifically, with an olefinic bond in a pre-determined position for further functionalization (Scheme Ib).[5] Stork has trapped the radical resulting from the intramolecular addition of a carbon radical to a double bond with tert-butyl isocyanide which decomposes to yield the chemically versatile nitrile substituent.[6] Marinovic and co-workers have recently extended Stork's work by intramolecular 1,5-addition of vinyl radicals to enones, which could be synthetically useful in forming gibberelic acid and terpenoids possessing anti-tumor and anti-fertility activity (Scheme Ic).[7]

Scheme I



These recent advances in radical cyclizations show the formation of 5,5-, 5,6-, or 6,6-bicyclic systems which result from competition between 1,5-cyclization and 1,6-cyclization. The pre-determined selection of a 1,5- or 1,6-cyclization was made possible by earlier mechanistic studies on 5-hexenyl radicals in which the influence of substituents on the reactivity and selectivity of the radicals was established (Scheme II).[1] Such radicals are frequently generated from an alkyl halide, an alkenyl halide, or a thioether with tributyltin hydride and azobis (isobutyronitrile), AIBN, in refluxing benzene, although other methods have been employed.[1c]

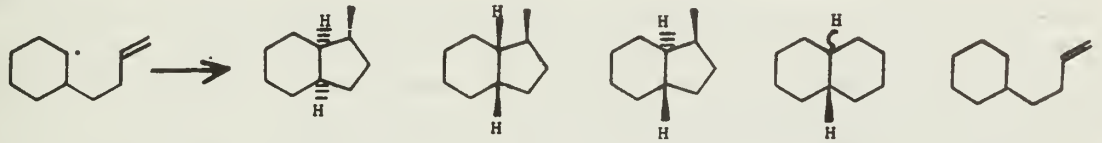
Scheme II



X = Br or SPh

The mechanism of addition of the radical to the alkene is believed to involve an early transition state which incorporates the three participating carbon atoms at the vertices of a triangle lying in a plane orthogonal to that of the olefin's σ framework. This geometry is dictated by the primary interaction of the semi-occupied 2p orbital (SOMO) with one lobe of the unoccupied π* orbital (LUMO).[8] In a radical cyclization under kinetic control this required disposition of centers is more readily accommodated in the exo transition state because of steric interactions (between C-2 and C-6 substituents in the chair endo transition state), stereoelectronic control (maximizing SOMO-LUMO interaction), and entropy effects (involving a smaller decrease in rotational entropy for a 5-membered ring).[1a] Beckwith has developed quidelines concerning the stereochemistry of substituents on the 1,5-hexenyl systems based on minimum energy of the chair transition state in which 1- or 3- substituted systems afford mainly cis-disubstituted products, whereas 2- or 4- substituted systems give mainly trans-disubstituted products.[1d] However, sometimes the geometrical constraints of bicyclic systems cause the formation of products with stereochemistry opposite that predicted by the 5-hexenyl system (Scheme III).[9]

Scheme III



3 (56%) 4 (16%) 5 (4%)* 6 (cis 0.7% trans 1.3%) 7 (22%)

*Expected major product

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STUDIES ON ALLYLIC PYROPHOSPHATE CYCLIZATION IN TERPENOID BIOSYNTHESIS

Reported by Han-Young Kang March 22, 1984

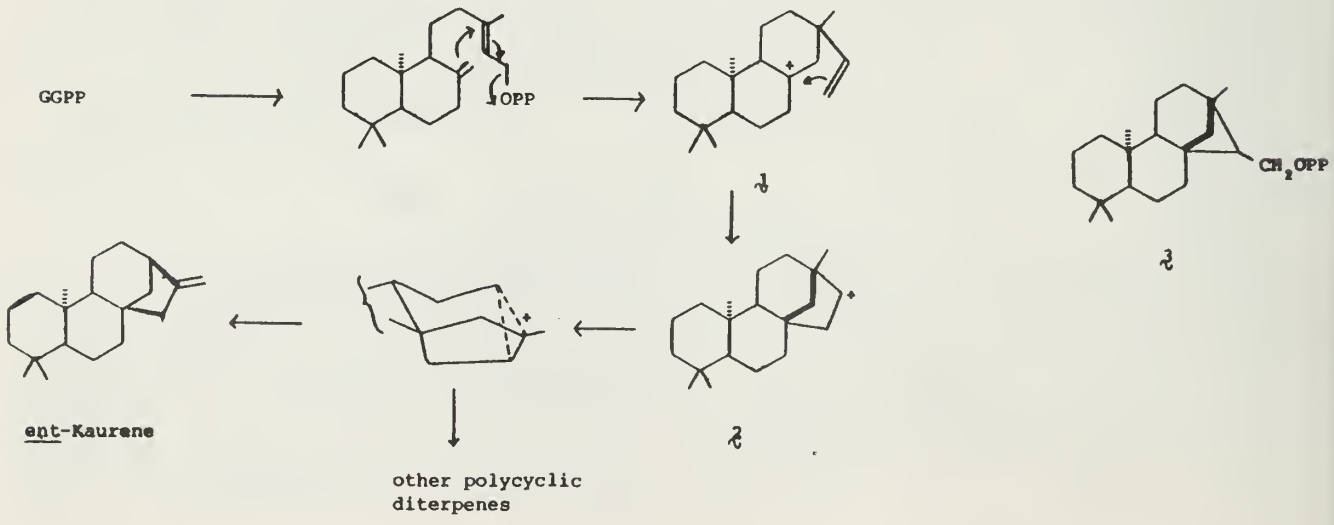
Geranyl pyrophosphate (GPP), farnesyl pyrophosphate (FPP), and geranylgeranyl pyrophosphate (GGPP) have been recognized as the universal precursors of cyclic mono-, sesqui-, and diterpenes, respectively. The details of the cyclization of these acyclic precursors constitute the heart of terpenoid biogenetic theory; however, they are still poorly understood and substantial disagreement remains.[1,2]

There have been several theories about the cyclization process. Recently a mechanism involving trans → cis isomerization via an intermediate tertiary allylic pyrophosphate (or via direct cyclization of the tertiary allylic pyrophosphate intermediate as a variant) has been proposed.[3,4] It was observed from studying the biosynthesis of a sesquiterpene, cyclonerodiol, that the enzyme-catalyzed isomerization of FPP to nerolidyl pyrophosphate took place with net syn stereochemistry, most probably by an ion-pair mechanism. The existence of a remarkably tight coupling of the pyrophosphate and terpenoid partners was reported from the study of the enzyme system which catalyzes the conversion of GPP to *d*-bornyl pyrophosphate.[5] Similar results have been observed in other enzyme systems.[6,7]

The currently accepted biogenetic pathway to kaurene (and other tetracyclic diterpenes), which was proposed by Wenkert[8], is shown in Scheme I. Studies have been carried out to test this mechanism by simulating the transformations, and considerable success has been achieved in generating beyeranyl and kauranyl cations.[9] However, there has not been much success in simulating the π-cyclization step (from 1 to 2 in Scheme I) of the pathway.[10-13]

A possible alternative to the biogenetically proposed 5-endo-trigonal π-cyclization (which seems inefficient due to poor orbital overlap and for thermodynamic reasons) would be a 4-exo-trigonal cyclization,[14] resulting in the system which could be represented by the cyclobutylcarbinyl pyrophosphate 3. Subsequent ring expansion of 3 would lead to the beyeranyl cation (2) and eventually to kaurene.

Scheme I



To test whether a 4-exo-trigonal cyclization is operating in the biosynthesis of kaurene, the preparation and enzymatic incubation of compound 3 is required. In the seminar the synthesis and behavior of cyclobutylcarbinyl compounds in chemical and enzymatic systems will be discussed.

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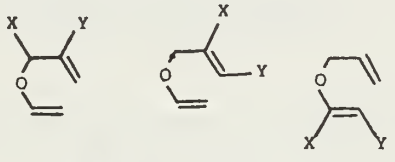
RATE ACCELERATION OF AN ALIPHATIC CLAISEN REARRANGEMENT DUE TO SUBSTITUENTS IN A PSEUDO PARA-RELATIONSHIP

Reported by Brian D. Rogers March 26, 1984

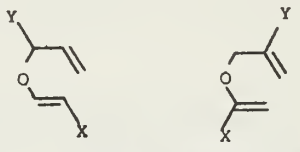
The Claisen rearrangement[1] of substituted allyl vinyl ethers to γ,δ-unsaturated carbonyl compounds has increased exponentially in value as a synthetic tool,[1a] as the conditions required for rearrangement have become milder and the range of included functionality has become broader. Recent theoretical[2] and experimental[3] studies of substituent effects on this [3,3]-sigmatropic rearrangement indicate that the placement of functionality is crucial to obtaining a maximum rate enhancement.

Carpenter[4] has proposed that a non-additive (synergistic) substituent effect may result when a pseudo ortho or pseudo para relationship exists between a π-donor and a π-acceptor group in an allyl vinyl ether (Scheme I), resulting in a faster rate of rearrangement than would be predicted from the effect of each substituent taken individually.

Scheme I



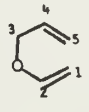
Possible pseudo ortho relationships



Possible pseudo para relationships

In accord with Carpenter's prediction, a large rate enhancement[5] recently has been shown to exist when an activating[5] ethoxy group and deactivating[5] π-acceptor (CN, CO_2Et, C=O) are present in the 3 and 1 position (Figure I) of an allyl vinyl ether, respectively. This rate acceleration, which may be predicted using Carpenter's delocalized transition state model, is most likely due to a "through resonance" interaction between the ethoxy and the π-acceptor substituents in the transition state. The effect of this interaction would be to stabilize the transition state relative to the ground state, the result being the observed rate enhancement.

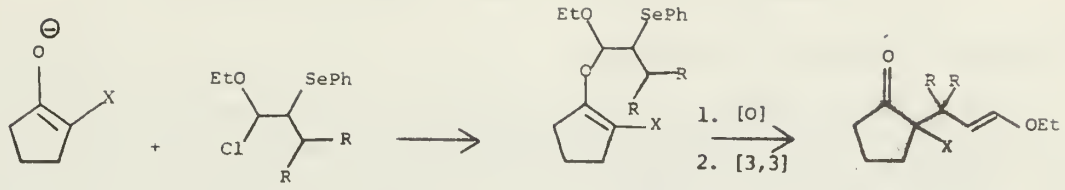
Figure I



The ease of rearrangement of this system was first demonstrated by Coates and Hobbs[6] and its preparation by enolate anion alkylation with a phenylseleno-substituted α-chloroether (Scheme II) followed by oxidative elimination of the phenylseleno group[7] allows the preparation and rearrangement to be conducted at room temperature.

Dimethyl substitution ($R=CH_3$) showed the joining of quaternary centers to be facile, albeit achieved in only moderate yield, and intramolecularity of the rearrangement was proven by a cross-over experiment. A small solvent-induced rate acceleration was also observed when the solvent was changed from [$^2H_6$]benzene to [$^2H_3$]acetonitrile.

Scheme II



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THE NUCLEAR OVERHAUSER EFFECT AS A TOOL FOR INVESTIGATING MOLECULAR COMPLEXES AND LARGE MOLECULES

Reported by Thomas C. Pochapsky March 29, 1984

The Nuclear Overhauser effect (NOE) and associated phenomena are the result of dipole-dipole (dd) interactions between nuclei situated near (<5Å) each other in space. Since dd interactions are through space, nuclei need not be J-coupled in order to interact with each other, and NOE provides a unique tool for investigating systems in which nuclei not necessarily part of the same molecule are close in space.

In the simplest NOE procedure, one resonance is saturated while the effect on the intensity of other resonances is monitored. As this experiment has been performed on many small molecules in order to establish conformations and structures, the theory and limitations of double irradiation NOE are fairly well established.[1] Extension to larger, more complex systems has been successful in some cases. Bergeron and co-workers have used NOE enhancements to study host-guest complexes of cycloamylose with several aromatic substrates in order to determine the orientation of the guest molecule within the cycloamylose cavity.[2,3] In this case, NOE enhancements were positive, indicating that the extreme narrowing case prevailed, that is, $(\omega_o\tau_c)^2 << 1$, where ω_o is the Larmor frequency of the observed nucleus and τ_c is the molecular correlation time, an indication of the rapidity of molecular tumbling.[1] As $\omega_o\tau_c$ increases enhancements become smaller and approach zero at $\omega_o\tau_c = 1.2$.[4] For systems with $\omega_o\tau_c > 1.2$ (i.e., very large molecules, low temperature or viscous solvent) NOE's are negative and relatively non-specific due to spin diffusion.

In order to compensate for this non-specificity, short irradiation times can be used, which limit the amount of spin diffusion occurring. Williams and co-workers used an saturation pulse of 200 ms to obtain specific negative NOE measurements on a actinomycin complex with a synthetic tetranucleoside duplex, d(A-G-C-T).[5] A similar process has been used successfully in the study of nicotinamide/lactate dehydrogenase complexes by Levy, using a frequency-specific irradiation pulse of 400 ms prior to FID acquisition.[6] Because short pulse widths tend to broaden saturation power curves, in dealing with crowded spectral regions another method, called truncated driven NOE (TOE), was used by Wüthrich and co-workers to assign amide proton resonances in a globular protein basic pancreatic trypsin inhibitor.[7] TOE involves the use of variable pre-irradiation times followed immediately by FID acquisition. In this case, the buildup of NOE, as determined by a graph of resonance intensities versus irradiation time, is directly related to the inverse sixth power of the internuclear distance, assuming only first-order effects.[8] TOE has also been used by Williams to determine the proton internuclear distances in the binding sites of vancomycin and ristocetin A complexes with cell-wall peptide analogs.[9]

In the aforementioned studies, all NOE's studied were proton-proton effects. NOE's, of course, can be observed between any nuclei with spins greater than zero, although, practically, heteronuclear NOE is limited by the proportionality, (see eq. 1) where $F_d(s)$ is the fractional enhancement of resonance corresponding the nucleus d upon saturation of the s resonance, and the γ_i's are the respective gryomagnetic ratios of those nuclei.[1] This usually limits studies to the saturation of a proton resonance while observing the effect on another nucleus (or another proton). This is

$$F_d(\theta) \sim \frac{\gamma_s}{2\gamma_d} \qquad \text{(Eq. 1)}$$

still very useful, as can be seen from examples cited. Watkins and co-workers used ^{13}C $\{^1H\}$ NOE to establish the tertiary structure of the cyclic peptide valinomycin.[10] They showed that saturation of specific amide proton resonances gave rise to enhancements not only of the carbonyl carbon of the amide unit on which that proton resides, but also of the carbonyl carbon in peptide residues to which the irradiated proton is hydrogen-bonded. Enhancement ratios were used to establish hydrogen bond lengths which, when coupled with other data, led to a tertiary structure assignment. In another case, Shibata has shown that the conformation of the polar head groups of phospholipids in inverted micelles can be established using ^{31}P $\{^1H\}$ NOE.[11]

Of all the developments in cross-relaxation techniques, the most exciting possibilities are to be found in two dimensional spectroscopy. 2D methods allow simultaneous determination of all cross-relaxation mechanisms between nuclei in large molecules and, coupled with other 2D methods such as COSY (correlated spectroscopy)[12] and SECSY[13] (spin-echo correlated spectroscopy), provide a powerful tool for investigating complex systems. In its simplest form, 2D NOE (NOESY) as described by Macura and Ernst,[14] involves a series of three 90° pulses, separated by waiting times t_1, t_{mix}, and t_2, the acquisition time. After the first pulse, the magnetization is tipped to the x-y plane, where precession at the respective Larmor frequencies spin-labels all resonances. The second pulse puts the net magnetization along the -z axis, and cross-relaxation takes place during t_{mix}. The third pulse recovers the transverse magnetization, which is detected during t_2. The FID, a function of t_1, t_2 and t_{mix}, is transformed to a function of ω_1,ω_2 and t_{mix} (representing intensities), which is plotted as the 2D spectrum. The usual one-dimensional spectrum may be represented along the x and y axes of the plot, and cross peaks (x,y) represent magnetization transfer from a nucleus with resonance x to a nucleus with resonance y. Many examples of applying 2D NOE to large systems already exist,[15,16] and in time the technique should become indispensable to the study of complex molecules.

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USE OF PHOSPHORUS COMPOUNDS IN THE SYNTHESES OF 1,1-DIFLUORO-1-ALKENES, 1-FLUORO-1-HALO-1-ALKENES, AND 1-FLUORO-1-ALKENES

Reported by Dean Hoglen April 5, 1984

The preparation of fluoroolefins is of interest owing to the known biological activity of fluorine-substituted compounds and the potential use of fluoroolefins as intermediates in organic synthesis.[1,2] The most effective methods of synthesizing 1,1-difluoro-1-alkenes, 1-fluoro-1-halo-1-alkenes, and 1-fluoro-1-alkenes make use of organophosphorus compounds as key reactants (Table).

Table. Comparison of Yields for Different Methods of Synthesizing 1,1-Difluoro-1-Alkenes.[3-7]

Starting Carbonyl R^1R^2CO	$ClCF_2CO_2Na$ Ph_3P	$ClCF_2CO_2Na$ $(n\text{-}Bu)_3P$	CF_2Br_2 $((CH_3)_2N)_3P$	CF_2Br_2 Ph_3P	CF_2Br_2 $(Me_2N)_3P,Zn$	CF_2Br_2 Ph_3P,Zn	CF_2Br_2 Ph_3P,Cd	$Ph_3\overset{+}{P}-\bar{C}R^1R^2$ HCF_2Cl	$LiCF_2P(O)(OEt)_2$
$CH_3(CH_2)_5CHO$	52	7						60	
cyclo-$C_6H_{10}O$	0	46						80	
cyclo-$C_6H_{11}CHO$		72	0		77	80			
C_6H_5CHO	74			65		76		60	
P-$O_2NC_6H_4CHO$	poor							trace	87
$C_6H_5COCH_3$		34.6	81		43	<5		60	
$(C_6H_5)_2CO$		13						57	64
$C_6H_5CH{=}CHCHO$				56	33			15	
C_6F_5CHO				20			62	trace	
$C_6H_5COCF_3$	75.9	0		85					
p-$H_3COC_6H_4COCF_3$	90.7			54			68		
m-$BrC_6H_4COCF_3$	2			83					
$C_6H_5COC_2F_5$	48			82					

*This method does not use a carbonyl compound. The ylide contains the same R groups as the carbonyl compounds used in the other methods.

A very effective method recently developed for the synthesis of 1,1-difluoro-1-alkenes involves the reaction of nonstabilized alkylidene and (arylalkylidene)triphenylphosphoranes with chlorodifluoromethane, yielding the desired fluoroolefins and products isolable for reuse (Equation 1).[3]

$$2Ph_3\overset{+}{P}-\bar{C}R^1R^2 + HCF_2Cl \rightarrow [Ph_3\overset{+}{P}CHR^1R^2]Cl^- + Ph_3P + F_2C{=}CR^1R^2 \qquad (1)$$

The most frequently used method for synthesis of fluorinated alkenes, however, is the Wittig reaction using (fluorohalomethylene)phosphoranes and (fluoromethylene)phosphoranes.[4,5] Methods using halogenated methanes as the source of the ylidene carbon are most effective (Equation 2), although

$$2R_3P + CFXY_2 + R_1R_2CO \rightarrow R_3PO + R_3PY_2 + R_1R_2C{=}CFX \qquad (2)$$
$$X,Y = F,Br;\ Br,Br;\ Cl,Cl$$

other sources of the ylidene carbon include trihaloacetates and phenyltrihalomethylmercury.[1g,4-6] A recently reported modification of the Wittig reaction uses the reaction of lithiated phosphonates (1) with carbonyl compounds to prepare 1,1-difluoro-1-alkenes and 1-fluoro-1-alkenes in good yields.[7] Other methods useful in the synthesis of specific types of fluoroolefins have also been developed.[8-10]

$$LiCXFP(O)(OR)_2 \quad X{=}H,F$$

1

The recent expansion of methods available for synthesis of vinyl fluorides gives greater scope in planning syntheses of fluorinated compounds, allowing not only further exploration of their biological activity but also providing more versatile use of such compounds as synthetic intermediates.

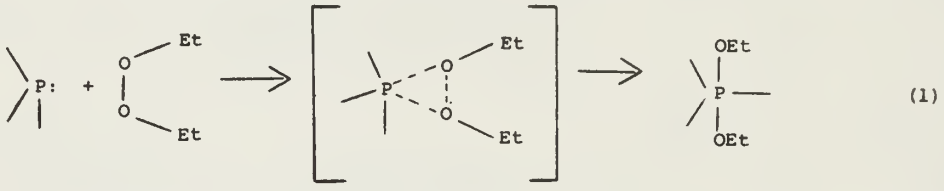
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BIPHILIC INSERTION REACTIONS OF PHOSPHORUS

Reported by Dennis Sagl April 12, 1984

The reaction of trisubstituted phosphines, R_3P, with diethyl peroxide to produce phosphine oxides, R_3PO, has been known for some time[1]; however, the intermediacy of phosphoranes, $R_3P(OEt)_2$, in that reaction[2] and the formation of pentaalkoxyphosphoranes, $(RO)_3P(OEt)_2$, by reaction of phosphites, $(RO)_3P$, with diethyl peroxide[3] are more recent discoveries. The formation of phosphoranes in these reactions can proceed via nucleophilic attack at oxygen to yield a phosphonium alkoxide, $(R_3POEt)^+EtO^-$, which then reacts to give the phosphorane, or by a concerted "biphilic" mechanism (Eq. 1) in which phosphorus inserts into the oxygen-oxygen bond of the peroxide.



(1)

Early studies on diethyl peroxide additions to phosphines[4] and phosphites[3] supported the concept of biphilic insertion. More rigorous studies of kinetic order, solvent effects, and activation parameters in the reaction of various cyclic phosphines with diethyl peroxide and in the reactions of phosphines with dioxetanes[6,7,8] provide further evidence for the biphilic insertion mechanism.

Following the initial report that phosphoranes are formed on reaction of diethyl peroxide with tricoordinate phosphorus, reactions of phosphorus compounds with other species containing weak σ bonds have been investigated. Evidence has been obtained which implicates a biphilic mechanism in the reactions of alkyl hypochlorites,[9] N-chlorodialkylamines,[10] certain disulfides,[11] and sulfenate esters[12] with various tricoordinate phosphorus compounds, although further studies on these systems are needed. In addition, a biphilic mechanism has been postulated for reaction of triphenylarsine and triphenylantimony with tetramethyl-1,2-dioxetane,[13] and a reversible insertion reaction has been observed.[14]

Reactions which proceed via biphilic insertion have proven to be useful in the synthesis of a number of phosphoranes, and the discovery that acyclic phosphoranes containing at least two alkoxy groups often undergo exchange with 1,2- and 1,3- diols to give cyclic alkoxyphosphoranes[15] has extended the utility of the reaction. Various phosphoranes prepared in this manner have proved useful in the study of phosphoranes containing highly strained rings,[11b] of intramolecular isomerization of cyclic phosphoranes,[11c,16] and of hexacoordinate phosphorus.[17] Furthermore, some of these phosphoranes have potential synthetic utility as alkylating agents,[18] as cyclodehydrating agents,[19] as epoxidizing agents,[20] and as a source of dienes generated by reverse cycloadditions.[21]

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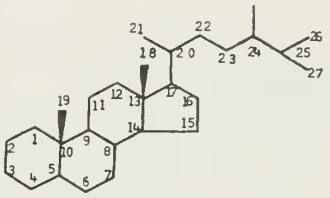
MICROBIAL TRANFORMATIONS OF ANTIBIOTICS

Reported by William C. Snyder

April 16, 1984

One of the earliest transformations of a complex organic compound was that of Peterson and Murray, who reported the oxidation of progesterone to 11α-hydroxyprogesterone in a single-step bioconversion using Rhizopus arrhizus.[1] The importance of this transformation lies in the site of hydroxylation, which is remote from any functional group. Although a few chemical methods exist for accomplishing remote transformations of steroids[2-4] microbial hydroxylation is available for virtually all sites of the steroid nucleus (Scheme I)[5] and is generally superior to chemical procedures.

Scheme I Steroid sites hydroxylated by microorganisms.



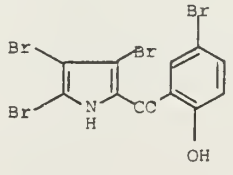
1α,1β,2β,5β,6β,7α,7β,9α,10β,12α,12β,14α,15α 15β,16α,16β, 17α,19,21,27.

Even before the hydroxylation of progesterone, Sakaguchi and Murao[6] reported an enzymatic hydrolysis for obtaining 6-aminopenicillanic acid from naturally occurring forms of penicillin. Many reviews exist to those interested in incorporating microbial transformations in the modification of natural and synthetic compounds.[7-13] The present report describes some of the techniques involved and transformations that can be achieved with microorganisms.

I. Techniques in Biotransformations

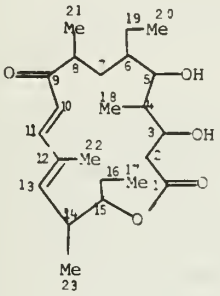
Supplementation of the Producing Organism. In 1945, Arnstein et al.[14] showed that in the presence of added p-hydroxyphenylacetic acid about 35% of the total penicillin produced in a surface culture was p-hydroxybenzylpenicillin, as opposed to 5% in the culture without added precursor. Similar results were obtained with N-(2-hydroxyethyl)-p-hydroxyphenylacetamide as a precursor.[15] This type of precursor addition allows the selected production of a particular metabolite over less desirable ones.

Other supplementations are designed not merely to enhance the production of metabolites already present but to bring about the elaboration of novel compounds. When bromide is added to fermentation broths of Actinosporangium vitaminophilum, an assortment of brominated pyrrolomycins results, of which pyrrolomycin-F_1 (1) is the most active.[16] The biological replacement of chlorine with bromine has also been accomplished for the antibiotics chlorotetracycline[17] and pyrrolnitrin.[18]

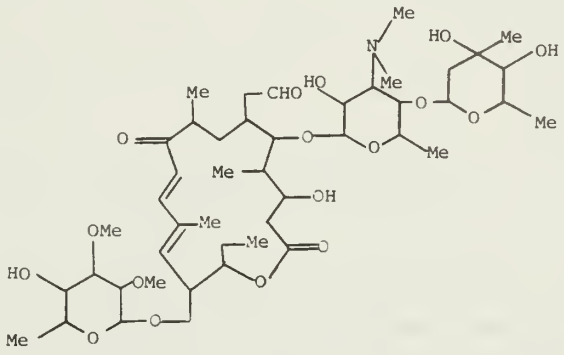


1

Mutation of the Producing Organism. Other methods of obtaining "transformed" antibiotics involve mutation of the producing organism. In this way, mutants of Streptomyces cattleya produced N-acetyl and dehydroxy carbapenems related to the thienamycins.[19] Another such transformation is the production of protylonolide (2) from a Streptomyces fradiae mutant no longer capable of tylosin (3) production.[20] This procedure has been used extensively for the production of novel macrocyclic antibiotics.[21-23] The resulting compounds are then used for synthetic manipulation or for futher biological transformation. Although macrolide aglycones can usually be obtained by acid hydrolysis, as is erythronolide A,[24] the production of earlier biosynthetic precursors of the aglycone by chemical manipulation of the antibiotic is virtually impossible.



2 (Protylonolide)

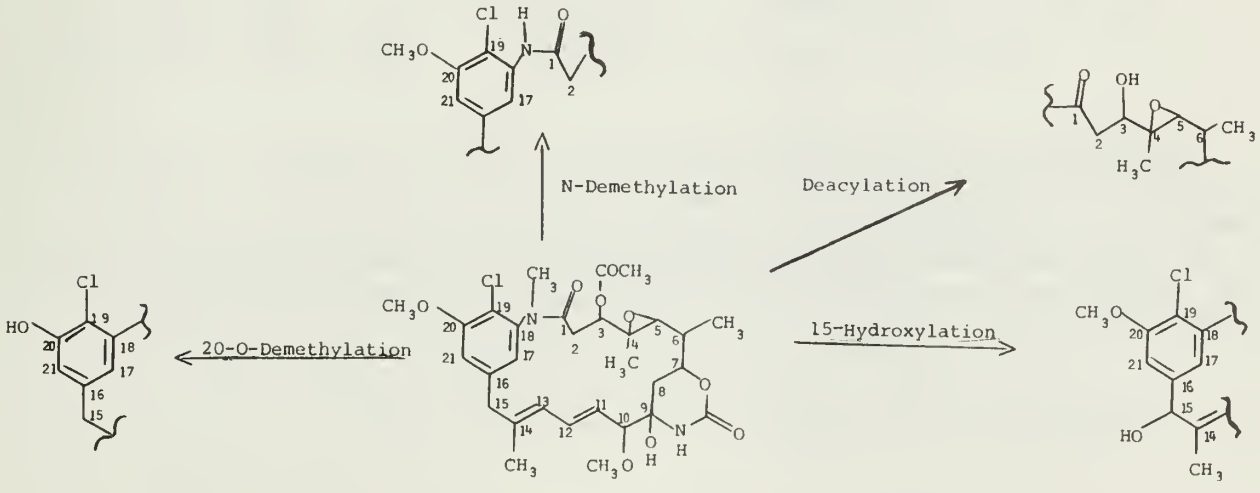


3 (Tylosin)

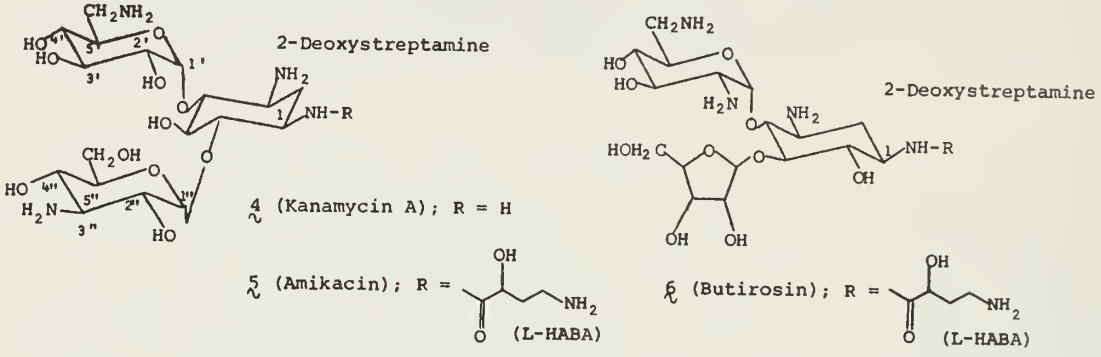
Mutasynthesis. In 1969, the first mutasynthetic antibiotics were reported by Shier and Rinehart.[25,26] The hybrimycins were produced by feeding streptamine and 2-epistreptamine to idiotrophs of 2-deoxystreptamine for the production of neomycin. Similarly, mutants of Streptomyces niveus incorporated modified coumarins into novobiocin.[27,28]

Substrate Addition to the Transforming Organism. The earliest forms of biotransformations involved the addition of the substrate to be modified to fermentations of the transforming organism. A recent example is found in the microbial conversions of the ansamitocins (Scheme II).[29-31]

Scheme II Microbial conversions of ansamitocin P-1.

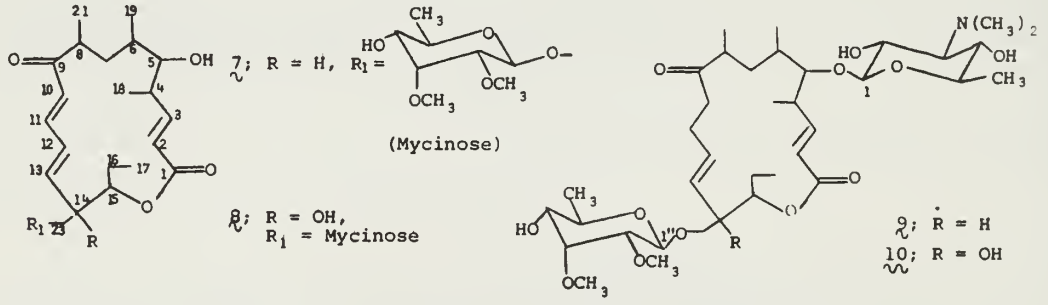


Hybrid Biosynthesis. The modification of a substrate by the biosynthetic machinery of a culture normally producing related materials is called hybrid biosynthesis. This is accomplished by mutating the transforming organism or adding inhibitors so that it no longer expresses its own products. Kanamycin (4) possesses a 2-deoxystreptamine group as does amikacin (5, biosynthetically derived from kanamycin), which also has an L-α-hydroxy-γ-aminobutyryl side chain on its 2-deoxystreptamine unit. Mutants of the bacterial culture unable to synthesize butirosin (6) acylate exogenous kanamycin.[32]



The addition of kanamycin to a gentamicin mutant resulted in the combimicins which are characterized by 4"-C-methylation as well as 3',4'-dideoxygenation in the kanamycin molecule.[33] The combimicins have superior Gram-positive and Gram-negative antibacterial activity to that of the kanamycin parent as well as reduced ototoxicity.

The methodology involved in hybrid biosynthesis can be extended to macrolides. The tylosin producer, Streptomyces fradiae, transforms dedesosaminylmycinamicin IV (7) to dedesosaminyl-5-O-mycaminosyl-10,11-dihydromycinamicin IV (9). Likewise, incubation with 8 resulted in 10.[34]



Protylonolide (2) has been transformed to the chimeramycins[35] and other hybrids[36] by the ingenious use of cerulenin, an inhibitor of the polyketide "condensing enzyme".[37] The use of the inhibitor prevents de novo synthesis of the aglycone without impairing glycosylation. The same procedure has been used in the transformation of tylosin by a spiramycin producer inhibited with cerulenin.[38]

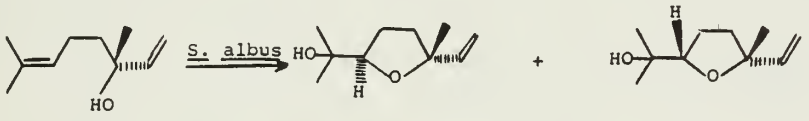
Enzymatic Conversions. The use of enzymes in pure or partially purified form is becoming increasingly important in organic synthesis. Enzymatic synthesis of α-aminobenzylpencilillin (ampicillin) was reported in 1971.[39] A 3-trifluoromethylcephalosporin derivative has also been prepared by this process.[40] A recent review on the use of enzymes in organic synthesis covers a large number of reaction types.[41]

II. Designing Transformations

Planning biotransformations with microorganisms requires little knowledge of the microbes and fermentation procedures. Several guides exist that include the methodology involved. The easiest way to achieve a desired transformation is to find an appropriate model system. This was done in the glucosylation of mycophenolic acid where two of the six cultures investigated successfully transformed the starting material.[42] Without proper precedent of analogous transformations, a desired biotransformation is likely to fail. An interesting attempt was made using protylonolide (2) as the substrate for a daunomycin producer. It was hoped that new daunosaminylated derivatives of protylonolide would be produced. Instead, hydroxylations occured at C-19 and C-23.[43]

Transformations modeled after biosynthetic mechanisms are extremely useful. The biosynthesis of polyether antibiotics employs an intermediate γ- or δ-hydroxy olefin, which cyclizes to form ethers. The transformation of linalool (11) by Streptomyces albus (Scheme III), a producer of the polyether nigericin, was designed with this in mind.[44]

Scheme III Transformation of linalool by Streptomyces albus.



11
3R(-)

(2R,5R)

(2R,5S)

III. Reactions Involved in Transformations

Hydrolysis. The aminocyclitol validamycin E (12) is converted to the more active validamycin A (13) by species of the genus Endomycopsis (Scheme IV).[45]

Scheme IV Conversion of Validamycin E to Validamycin A.



12 (Validamycin E)

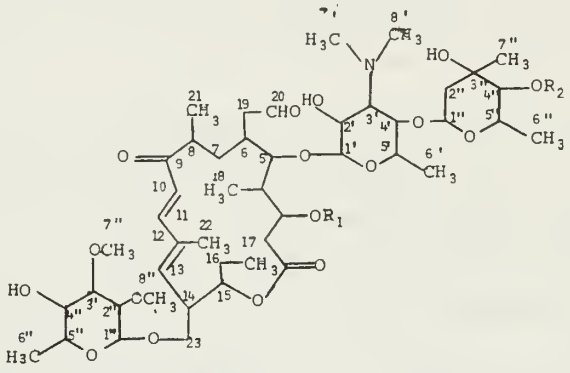
13 (Validamycin A)

Several cephalosporins have been hydrolyzed to 7-aminodeacetoxycephalosporanic acid. However, the D-α-aminoadipoyl chain on the 7-position of the cephem nucleus has evaded simple deacylation by enzymes. Such a transformation would greatly facilitate the production of semisynthetic cephamycins and cephalosporins. With this in mind researchers have studied the conversion of cephamycin C by a D-amino acid oxidase to the glutaryl-derivative, which is a substrate for deacylation by penicillin acylase.[46] Other β-lactams include nocardicin C, which has been hydrolyzed to 6-aminonocardicinic acid.[47]

Deacylation is also useful in the resolution of enantiomeric mixtures obtained in organic syntheses.[48] Total syntheses of natural products involving enantiomeric resolution by commercially available acylases are becoming routine.[49-50]

Acylation-Glycosylation. The degree of antibacterial activity of 16-membered macrolides and the blood levels achieved are influenced by the 3- and 4"-O-acyl groups.[51] With this in mind, the 3- and 4"-hydroxyl groups of the leucomycins were acylated by a strain of Streptomyces thermotolerans.[52] Similarly, the addition of tylosin and amino acid precursors of the acyl side chains to S. thermotolerans resulted in the formation of numerous acyl derivatives (Scheme V).[53]

Scheme V Acyl derivatives of tylosin.

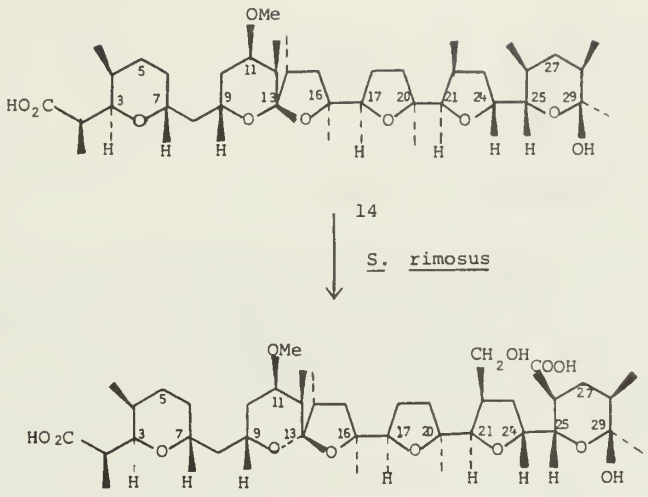


Compound	R_1	R_2
Tylosin	H	H
3-Acetyltylosin	$COCH_3$	H
3-Propionyltylosin	$COCH_2CH_3$	H
4"-Butyryltylosin	H	$COCH_2CH_2CH_3$
4"-Isovaleryltylosin	H	$COCH_2CH(CH_3)_2$
3-Acetyl-4"-butyryltylosin	$COCH_3$	$COCH_2CH_2CH_3$
3-Acetyl-4"-isovaleryltylosin	$COCH_3$	$COCH_2CH(CH_3)_2$
3-Propionyl-4"-butyryltylosin	$COCH_2CH_3$	$COCH_2CH_2CH_3$
3-Propionyl-4"-isovaleryltylosin	$COCH_2CH_3$	$COCH_2CH(CH_3)_2$

Microbial glycosylation of various antibiotics has been reported.[42,54] Both α- and β-D-glucosides of validamycin A have been prepared.[55] Biotransformations of the chemically derived erythronolides by mutant strains include glycosylation with oleandrosyl and desosaminyl units from an oleandomycin-blocked mutant.[56] Hybrid antibiotics have also been derived from lankamycin, darcanolide, and 11-acetyllankolide[57] in addition to various glycosylated platenolides[58,59] and rosaranolides.[60]

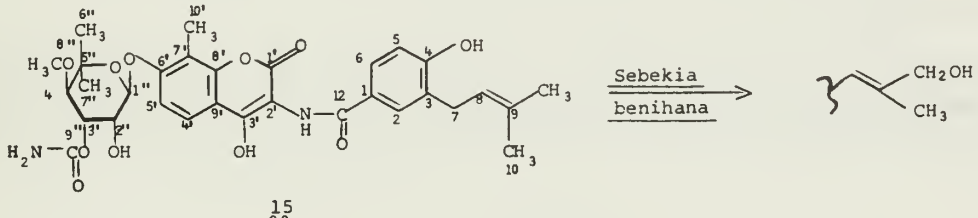
Oxidation. The introduction of a hydroxyl group to the skeleton of steroids has already been discussed. The C-22 methyl of grisorixin (14), an ionophoric polyether antibiotic, is converted by Streptomyces rimosus to a hydroxymethyl group. The C-26 methyl is also transformed to a carboxylic acid (Scheme VI).[61]

Scheme VI Biotransformation of grisorixin.

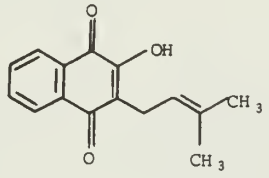


Novobiocin (15), a coumarin antibiotic, when added to cultures of Sebekia benihana, is transformed in 9% yield to the allylic alcohol (Scheme VII).[62] Since the product is an allylic alcohol, the same transformation could be accomplished chemically with selenium dioxide in 31% yield. However, the organism also converts 8,9-dihydronovobiocin to the alcohol, whereas only novobiocin can be oxidized chemically. A similar hydroxylation occurs with lapachol (16).[63]

Scheme VII Hydroxylation of novobiocin.

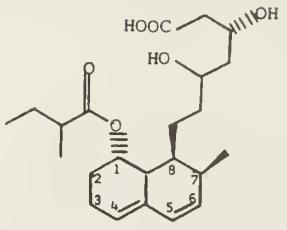


15



16

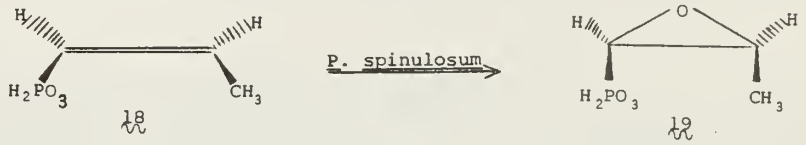
Microbial hydroxylation of compactin (17) provides a good example of directed screening for a desired product. Compactin is a competitive inhibitor of HMG-CoA reductase. In vivo, this inhibition results in the lowering of serum cholesterol. Recently, the sodium salt of 3-hydroxycompactincarboxylate (isolated as a minor mammalian metabolite of compactin) has been found to be more potent than the parent in the inhibition of HMG-CoA reductase. A 44% yield of 3β-hydroxycompactin was isolated from biotransformations with Mucor hiemalis.[64] Hydroxylation with Syncephalastrum nigricans was found to give 3α-hydroxycompactin exclusively.[65] Additional hydroxylations have since been reported giving 6α-hydroxy-iso-compactin, containing a 3,5-diene system.[66,67]



17 (Compactin, acid form)

Preparation of fosfomycin (19) via cis-propenylphosphonic acid (18) was accomplished in 90% yield by stereospecific epoxidation with Penicillium spinulosum as the transforming organism (Scheme VIII). This compares with a yield of less than 50% for the reported chemical synthesis.[68]

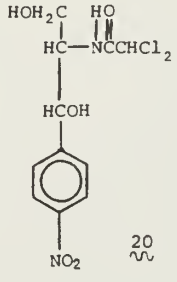
Scheme VIII Preparation of fosfomycin.



18 19

Reduction. Although yeasts have routinely been used in the reduction of β-oxoesters, reports of other transforming organisms are beginning to appear. In at least one example, Thermoanerobium brockii was found to give stereochemistry opposite to that predicted by Prelog's rule, typically observed in yeast reductions.[69] Reduction of the steffimycin[70] and rubeomycin[71] aglycone in addition to reduction of the safframycins[72,73] (along with decyanation) have been observed.

The reduction of nitro groups by microorganisms is often superior to synthetic manipulations when sensitive functionalities are present. An early example is the reduction of chloramphenicol (20) to its amino analog.[74]

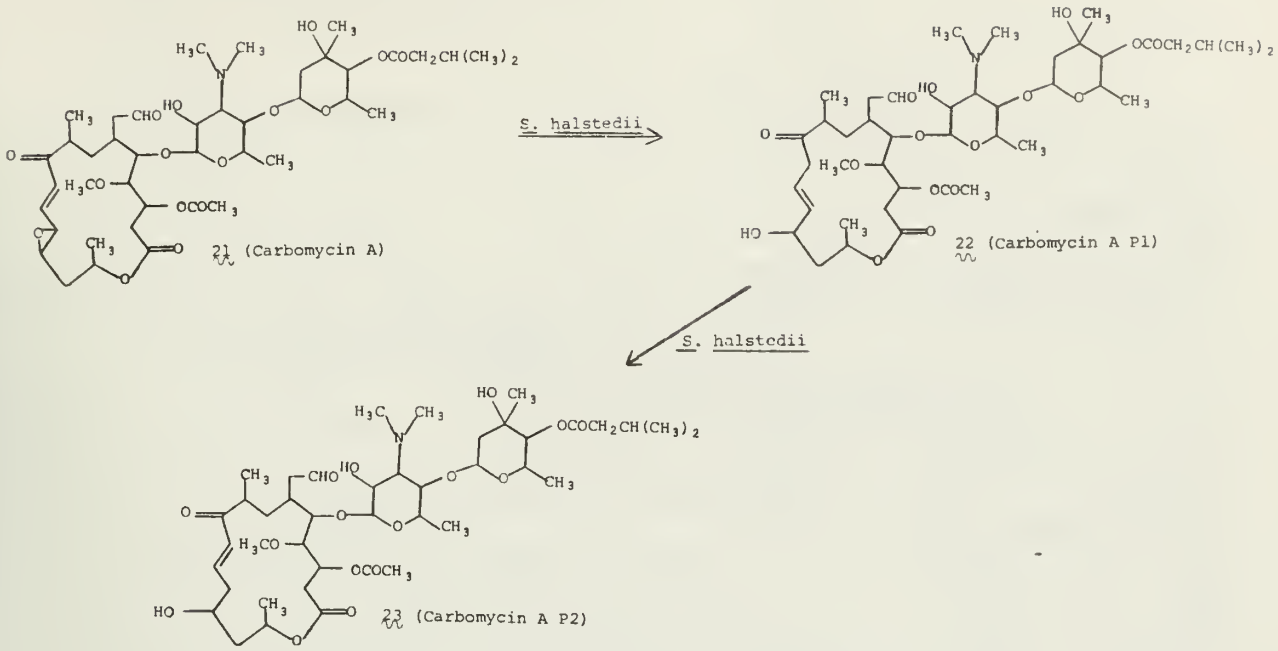


20

Microbes are also capable of simple epoxide reduction. Many examples have recently been reported for macrolides.[75,76] In one transformation, carbomycin A (21) was converted by Streptomyces halstedii subsp. deltae to (22) and (23) (Scheme IX). While 23 has superior in vivo activity against Staphylococcus aureus, dissolving metal reductions gave only 22.[77]

Hydrogen addition to double bonds is readily accomplished but has no advantage over catalytic methods. Recent examples include albocycline transformation by Streptomyces venezuelae[78] and the conversion of aclacinomycin A to aclacinomycin Y.[79]

Scheme IX Conversion of carbomycin A by S. halstedii.



Miscellaneous Reactions. Demethylation (N-, O-) is a valuable biomodification as already seen in the transformation of the ansamitocins Scheme II). Although rare, C-demethylation is also known to occur.[80]

An interesting transformation designed from a biosynthetic mechanism is the ring expansion of penicillin N to deacetoxycephalosporin C.[81,82] This work was carried out with mutants of a cephalosporin producer.[83]

Daunomycin is one of the most active antitumor agents presently in use. Interconversions of the aclacinomycins, auramycinone, and daunomycinone have utilized blocked mutants of various anthracycline producers.[84-90] Reviews of microbial transformations of anthracycline antibiotics and other antitumor agents are available.[91,92]

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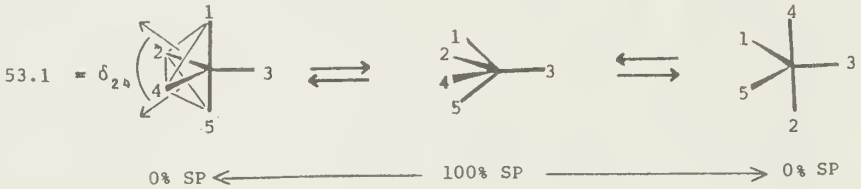
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FACTORS WHICH STABILIZE THE SQUARE PYRAMID IN PENTACOORDINATE MAIN GROUP ELEMENTS

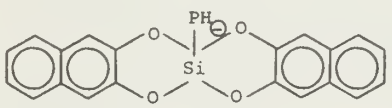
Reported by Charles F. Kahle, II April 19, 1984

An interesting feature of pentacoordinate main group elements is their stereochemical nonrigidity.[1] One of the earliest examples studied was phosphorus pentafluoride. To temperatures as low as -190°C only a doublet is observed in its ^{19}F NMR spectrum (due to P-F coupling, J_{P-F} = 916 Hz).[2] Berry proposed a process of intramolecular pseudorotation (Scheme I)[3] based on the normal vibrational modes of molecules with D_3h symmetry to explain the equivalence of the fluorine atoms in the spectrum. The transition state, which resembles a square pyramid (SP), is close in energy to the trigonal bipyramid (TBP) ground state ($\Delta G^{\ddagger}$ = 3.41 kcal/mole).[4]

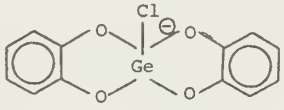
Scheme I



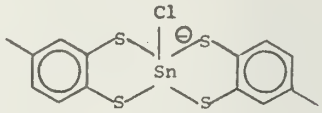
Many pentacoordinate structures have been determined by x-ray diffraction to lie somewhere on the pathway of Scheme I.[5a,b] Holmes has used the dihedral angle (δ_{24}) formed between normals to the faces 124 and 245 to represent the structural distortions of these molecules.[5b] A dihedral angle of 53.1° represents an idealized TBP (0% SP) and that of 0° an idealized SP (100% SP). Recently, structures close to 100% square or rectangular pyramidal (RP) have been determined for siliconates,[5a,6] germanates,[7] stannates,[8] phosphoranes,[9] arsoranes,[10] and antimoranes.[11]



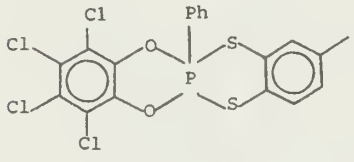
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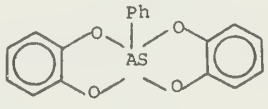
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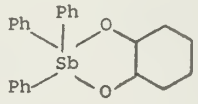
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97.4%



99.2, 94.8%



85.3%

In cases where H-bonding is not a factor, lattice effects are not believed to play a significant role in the structures observed.[12] Holmes has demonstrated that the IR and Raman spectra of solid- and solution-phase phosphoranes are very similar.[13] Maciel has compared the solid- and solution-phase ^{31}P chemical shifts of phosphoranes and found them to be very similar as well.[14] The fact that structural preferences correlate with substituent effects is additional evidence for the diminished role of lattice effects in determining the geometries observed.[15a,b]

Inspection of the highest occupied molecular orbitals for PH_5 suggest that four σ electron-withdrawing basal ligands and a σ electron-donating, π electron-withdrawing apical ligand will best stabilize the SP structure

relative to the TBP.[16] Electronic considerations of the ligands alone, however, are not enough to stabilize the SP relative to the TBP. Known examples of acyclic and monocyclic siliconates, phosphoranes, and arsoranes are much closer to the TBP in geometry than the SP or RP.[6,10,12] Holmes has demonstrated, in accord with x-ray data, that the RP can be stabilized by incorporating two unsaturated five-membered rings attached to the central atom by highly electronegative heteroatoms such as nitrogen, oxygen, or sulfur.[17] The extra stabilization is attributed to relief of ring strain brought about by differences in axial-equatorial bond lengths in the TBP. Increasing the steric bulk of the apical ligand also increases the percent displacement toward the RP.[18]

The factors which stabilize the SP or RP in phosphoranes apply to other Group IV A and V A central atoms.[5a,6,7,8,10,11] Based on x-ray structural information and dynamic NMR studies, Holmes suggests that the percent displacement toward the SP or RP increases as the rigidity of the central atom decreases (Sb>As>P and Sn>Ge>Si).[10,12]

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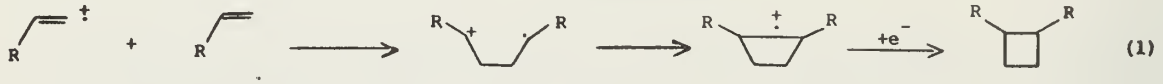
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CYCLOADDITIONS VIA OLEFIN RADICAL CATIONS

Reported by Glenn C. Calhoun April 23, 1984

Cycloadditions play an important role in carbon-carbon bond formation in organic synthesis. Recently, improving understanding of radical ion chemistry[1] has led to an investigation of cycloadditions via radical cations. This method is appealing because it has the possibility of proceeding by a chain mechanism and it may also be useful in the cycloadditions of electron-rich olefins.

To date there are relatively few cycloadditions that are believed to proceed through radical cation intermediates. The first such reaction was the dimerization of N-vinylcarbazole by Ledwith.[2] The reaction has been achieved with inorganic one-electron oxidants[3] and by photosensitization with electron acceptors[4] in polar solvents. The data obtained are consistent with a radical cation mechanism (Eq. 1).



(1)

Other workers have also obtained 2 + 2 cyclodimerizations photosensitized by electron acceptors. Dimerizations of vinyl ethers[5,6a], indenes[6], and p-methoxystyrene[7] have been proposed to proceed by radical cations. All of these dimerizations are more regiospecific than dimerizations via the triplet state. Indene and 1,1-dimethylindene give head-to-head dimers exclusively in the radical cation reaction. The corresponding triplet reaction gives a mixture of head-to-head and head-to-tail dimers. This regiospecificity has been rationalized by the preferential addition to form the most stabilized 1,4-radical cation. This, along with quenching of dimer formation by substances with lower oxidation potentials[6a] and nucleophiles,[8] and a dependence on solvent, provide evidence in favor of radical cation intermediates. CIDNP[9,10] and theoretical calculations[11] also lend support for this mechanism.

A few mixed reactions of one radical cation with a different olefin are also known.[6a,b,12] It appears that reaction of the radical cation with a more nucleophilic olefin may be necessary.

4 + 2 Cycloadditions are also known for radical cation reactions. The γ radiolysis of 1,3-cyclohexadiene (CHD) leads to 4 + 2 and 2 + 2 dimers of CHD.[13,14] The 4 + 2 dimers are believed to come from the CHD radical cation, while the 2 + 2 products are from triplet CHD.

Arnold and coworkers have found a 70% yield of 1,1,4-triphenyl-1,2,3,4-tetrahydronaphthalene from the photosensitization of 1,1-diphenylethene by electron acceptors.[8] Farid has found similar results using 9,10-dicyanoanthracene and 1,1-diphenylethene[15] or 2,6,9,10-tetracyanoanthracene with phenylacetylene.[16] Supression of dimers and formation of ethers in the presence of alcohols in consistent with a radical cation mechanism. Arnold has also been able to obtain cycloaddition products of 1,1-diphenylethene radical cation with other olefins.[17]

Another interesting development is the dimerization of CHD in methylene chloride using tris(p-bromophenyl)aminium hexachlorostibnate.[18] A 70% yield of 4 + 2 dimer was obtained at 0°C in 15 minutes. This reaction has been explained in terms of a radical cation chain mechanism. Mixed cycloadducts have also been prepared by this method, and have exhibited interesting chemo-, regio-, and stereoselection.[18,19] FMO, MINDO/3, and MNDO calculations[19-21] have all been used to rationalize the unique products and increased rate. Unfortunately, a recent report has cast doubts about the general applicability of this method in the presence of several functional groups.[22]

Although the scope of radical cation cycloadditions is not yet known, these results provide significant interest to both mechanistic and synthetic chemists.

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PHOTOACTIVATION OF REMOTE FUNCTIONAL GROUPS IN BICHROMOPHORIC MOLECULES

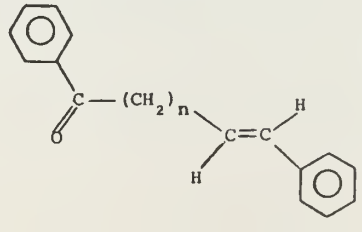
Reported by Tsuei-Yun Liang April 26, 1984

The photochemistry of the more common monochromophores (aromatic, ketone, ester, olefin, halogen, nitro, etc.) is well understood, while the photochemical consequences of irradiating molecules containing two or more functional groups is still a young science and not fully understood. Two chromophores in one molecule separated by a certain number of atoms which provide no important interactions in the ground state can substantially change the photochemical properties of the respective chromophores. In recent years, photochemists have begun to systematically survey interchromophoric interaction[1] in polyfunctional molecules, including aryl-olefin, aryl-acetylene, aryl-ester, aryl-amide, aryl-chloride, aryl-ketone and keto-olefin groups. These intramolecular interactions depend on the separation and relative orientation of the two remote functional groups.

This report treats two different classes of bifunctional molecules: 1) bifunctional acyclic compounds in which the two chromophores are joined by a non-rigid chain, with varying distance and orientation, and 2) cyclic molecules in which the two chromophores are coupled by a rigid link imposing more restrictions on distance or orientation. Several processes including 1) triplet energy transfer, 2) singlet exciplex formation, 3) singlet energy transfer and 4) enhanced triplet radiationless decay in the former systems will be discussed. In the latter systems, the stereochemical and regiochemical requirements for excitation transfer will be examined. The excitation transfer can be monitored by absorption, fluorescence (wavelength efficiency, lifetime), phosphorescence (wavelength, efficiency) and photoelectron spectroscopy.

Flexible bichromophoric systems. Flexible systems provide a time-dependent spectrum of interchromophoric relationships which give rise to "pre-excitation" and "post-excitation" interactions. They may also be used to obtain rate constants for bond rotation in the chain.[2]

The photochemistry of compounds containing an acetophenone chromophore and a trans-β-methylstyryl chromophore separated by two to four methylene groups has been studied.[3] UV spectra of these three compounds (1a, 1b and 1c) are very similar to the UV spectrum of an equimolar mixture of acetophenone and trans-β-methylstyrene, which indicates that the two chromophores are essentially non-interacting. In addition to trans-cis isomerization observed for each compound, compounds 1b and 1c were also found to give Norrish type-II cleavage products on photolysis but with very low quantum efficiencies. Excitation to the n-π* singlet state of an acetophenone chromophore is followed by very rapid and completely efficient intersystem crossing to the n-π* triplet state, as noted by Hammond and Wagner.[4] The triplet states may dissipate their excitation energy in three different ways: 1) γ-hydrogen abstraction to initiate the Norrish type-II photoelimination sequences; 2) intersystem crossing to the ground state; and 3) energy transfer to the β-methylstyryl chromophore. The kinetic data[3] are consistent with unit efficiency (ϕ_{et} = 1) in the triplet energy transfer to the trans-β-methylstyryl chromophore and in excellent agreement with the value measured for β-methylstyrene triplets by Hammond.[5]



1a: n = 2
1b: n = 3
1c: n = 4

Intramolecular triplet energy transfer is also observed in 1-phenyl-2-butene[6] and 5-phenyl-2-pentene[7] systems. The ground state and lowest singlet excited states of 1-phenyl-2-butene are relatively unperturbed, despite the two functional groups lying close in space, as indicated by relevant absorption, photoelectron[8] (8.75, 9.25 eV), fluorescence (efficiency, $\phi_f = 0.11$; lifetime, $^1\tau = 26$ nsec), and phosphorescence spectral data. Highly efficient cis-trans isomerization of 1-phenyl-2-hexene ($\phi_{C\rightarrow T} = 0.20$; $\phi_{T\rightarrow C} = 0.16$) must involve intramolecular triplet energy transfer, since added 2-hexene neither quenches the reaction nor is itself isomerized and 1,3-pentadiene, an excellent triplet quencher ($E_t \sim 59$ kcal/mole), is also not isomerized.

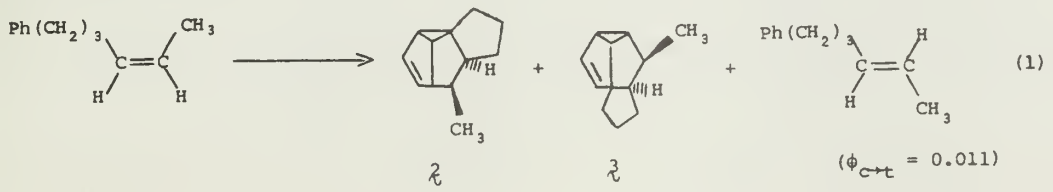
Although an extra methylene group separates the phenyl and olefinic groups for 5-phenyl-2-pentene, which might cause the intramolecular energy transfer to decrease, free rotation between the two methylene groups allows the π-electron clouds of the phenyl and olefin groups to come close together or to collide to undergo efficient intramolecular triplet energy transfer.

Rate constants for intramolecular triplet energy transfer (k_{et}) can be obtained by quenching experiments, which are summarized in Table I. The rate constant decreases in going from 1a to 1c; that is interpreted[3] by noting that the number of conformations in which the two chromophores nearly contact one another decreases greatly with an increasing number of methylene groups.

Table I. Rate Constants of Triplet Energy Transfer

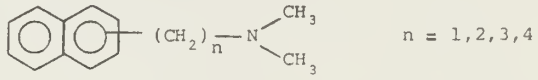
Compound	k_{et} (s^{-1})
1-phenyl-2-butene[6c]	$>3.6 \times 10^9$
5-phenyl-2-pentene[7]	6.0×10^7
trans-1,4-diphenyl-3-buten-1-one (1a)	7.2×10^{10}
trans-1,5-diphenyl-4-penten-1-one (1b)[3]	1.1×10^{10}
trans-1,6-diphenyl-5-hexen-1-one (1c)[3]	3.3×10^9

6-Phenyl-2-hexene displays different photochemistry from that of 1-phenyl-2-butene and 5-phenyl-2-pentene. Internal cycloaddition ($\phi_{2+3} = 0.25$) is the primary reaction from photolysis of 6-phenyl-2-hexene[9] (Equation I). The cycloadducts (2 and 3) arise from 1,3-addition to the aromatic ring. The UV absorption and photoelectron spectra give no evidence for appreciable ground state interaction. However, the fluorescence spectrum, though similar to that of hexylbenzene in appearance, shows a remarkable (94%) reduction in intensity and no phosphorescence is observed. The marked diminuation is not observed at 77 °K in an ethanol glass. This phenomenon can be attributed to intramolecular exciplex formation resulting from interaction between the phenyl excited singlet-state and the ground-state olefin. Quenching experiments, wavelength dependence for cycloaddition and retention of configuration at the reacting π bond are consistent with the involvement of a singlet rather than a triplet species. The rate of complexation ($^1k_{ex} = 1 \times 10^9$ sec^{-1}) is identical to the reported value[1] for the rate of rotation about a trimethylene chain.



2 3 ($\phi_{c\rightarrow t} = 0.011$) (1)

Intramolecular exciplex formation in naphthylalkylamines (4, n = 1 to 4) has been observed by Chandross and Thomas.[10] The maximal interaction was for n = 3. Chandross and Thomas concluded that this interaction is of the dipole-dipole type and not of the charge-transfer type.[11] Charge-transfer exciplex formation was observed in the anthracene-$(CH_2)_3$-p-N,N-dimethylaniline system[1] by Chuang. Other examples of intramolecular excimer and exciplex formation have been reported[12] for systems of the type of $Ar-(CH_2)_n-Ar^1$, especially with n = 3 ("n = 3 rule").

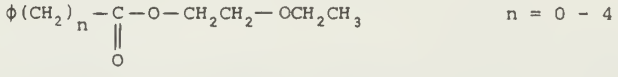


n = 1,2,3,4

4

5-Hepten-2-one[13] resembles 6-phenyl-2-hexene in its photophysical and chemical properties. Ketone-olefin cycloaddition and trans-cis isomerization of an olefin were observed. The rate of exciplex formation was $^1k_{ex} \leq 2 \times 10^{10}\ S^{-1}$ compared to $^1k_{ex} = 1 \times 10^9\ S^{-1}$ for 6-phenyl-2-hexene, in which the two chromophores are separated by an additional methylene unit ("n = 3 rule"), so the intramolecular excited state complexation is not restricted solely to n = 3.

Brainard and Morrison[14] observed intramolecular singlet energy transfer in system 5. Only the phenylacetate homolog (n = 1) shows appreciable photoreactivity ($\phi_{acid} = 0.098$). Norrish type-II cleavage of the phenyl-acetate can be quenched by cis-1,3-pentadiene at the same rate as fluorescence quenching.

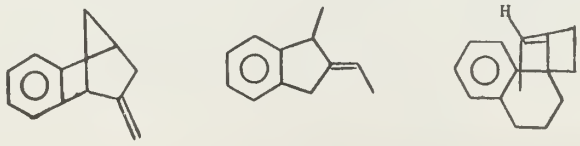


n = 0 - 4

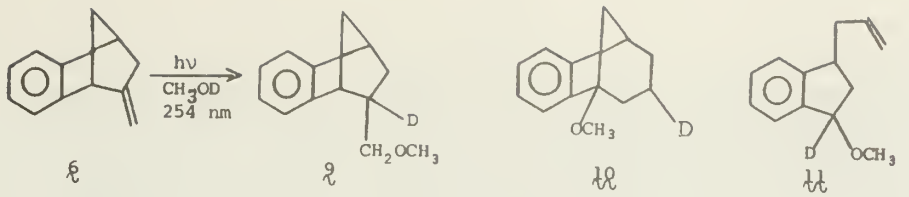
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Enhanced triplet radiationless decay competitive with triplet energy transfer can be determined by heavy-atom perturbation.[15] Only 29% of the triplet decay was observed in 1-phenyl-2-butene without isomerization about the double bond. Obviously enhanced triplet radiationless decay was found in cyclic compounds (vide infra).

Rigid systems. Rigid molecules provide information on intramolecular interactions as a function of well-defined interchromophoric and angular relationships.[16] Morrison and co-workers[17] have studied three well-defined nonconjugated aryl-olefins (6-8) with varied interorbital angles between the chromophores. The photochemistry of this system has proven to be remarkably varied, with participation by both singlet and triplet excited states, and solvent polarity plays a major role in determining the course of reaction. Compound 6 reacts primarily via a "diverted di-π-methane" reaction in hexane, rationalized by a deuterium-labeling experiment (Scheme I). Singlet and triplet states[17] anticipated in these reactions have been determined by xenon perturbation.[15] The extensive nonradiative decay[17] from the singlet and triplet states in 6 and 7 have been observed by heavy-atom perturbation methods. The singlet interations between the chromophores, deduced from photoelectron, absorption and emission spectroscopy, are a function of geometry, while the orthogonally arranged chromophores in 8 give rise to very little aryl singlet perturbation.

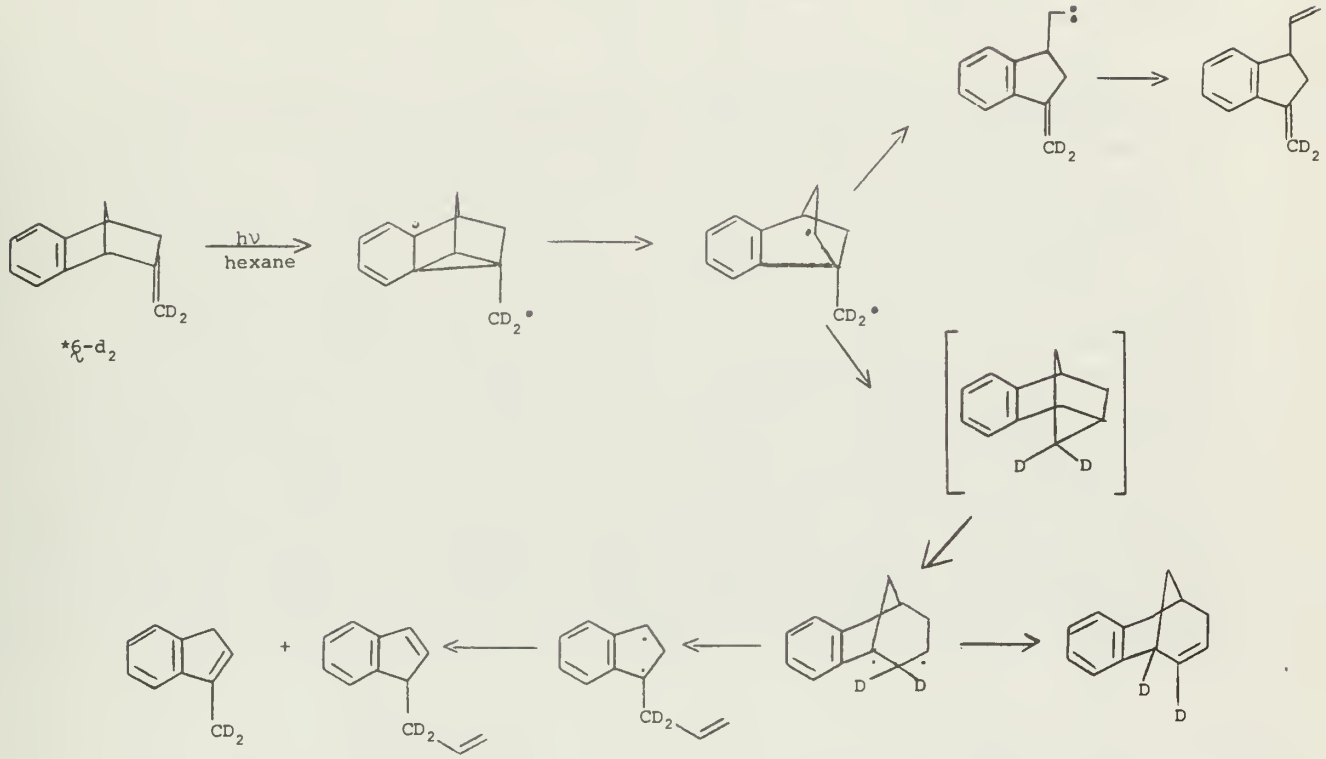


6 7 8



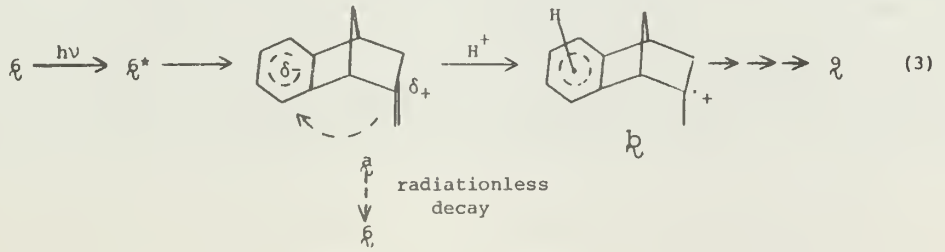
6 9 10 11 (2)

Scheme I



A novel photochemical phenomenon is observed on irradiation of 6 in methanol[18] in which three photoproducts, 9, 10 and 11 are formed (Equation 2), with the principal product (9) resulting from anti-Markovnikov addition of solvent across the double bond. Xenon perturbation and xylene sensitization[18b] studies confirm that compound 9 is derived from a singlet state while compounds 10 and 11 are derived from both singlet and triplet states. Acid catalyzes the photoaddition of solvent to 6 but does not quench the fluorescence of 6. The non-linearity of plots of ϕ vs. $[H^+]$ and linearity of ϕ^{-1} vs. $[H^+]^{-1}$ argue that protonation occurs after rather than before excitation.

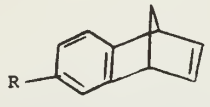
The marked enhancement of solvent addition when the electron affinity of the aromatic ring is increased by CF_3 substitution (ϕ increases by 60%) or the ionization potential of the olefin is lowered by methyl substitution (an 8-fold increase in ϕ), and the complete lack of addition or fluorescence quenching when a methoxyl group is on the aromatic ring are rationalized[18d] by a singlet-state interaction involving charge transfer polarization from the double bond to the aromatic ring (a) followed by a proton-assisted electron transfer, forming the radical cation (b) (Equation 3).



(3)

In the absence of acid, or in the case of molecules for which proton-assisted electron transfer is not competitive, the initial charge-transfer process provides a facile radiationless decay which can appreciably shorten the singlet-state lifetime. This singlet decay via a is to be distinquished from the sandwich-complex decay of 6-phenyl-2-hexene, which has no acid-catalyzed addition of methanol across the double bond. Besides the singlet decay, compounds 6 and 7 display triplet radiationless decay analogous to 1-phenyl-2-butene. A small perturbation of the $^1B_{2u}$ transition by the double bond[19] has been observed by circular dichroism studies.

A variety of meta-substituted benzonorbornadienes[20] (12) have been shown to undergo triplet-sensitized di-π-methane rearrangement with regioselectivity. In the case of acceptor substituents (R = NO_2, $CO_2C_2H_5$, CN and $COCH_3$), benzyl-vinyl bridging at the para position of the aryl ring 13 (Equation 4) was observed, while in the case of donor substituents (R = OCH_3, NH_2 and F), meta bridging to give 14 was noted (Equation 5). These effects of donor and acceptor groups have been explained by a molecular ortibal model.[20b,21] The interaction of the half occupied LUMO of the excited aromatic group with the vacant LUMO of the ground state ethylene group is preferred at the carbon having the highest electron density. The ortho-substituted benzonorbornadienes[22] also undergo triplet-sensitized di-π-methane rearrangement with preferential benzyl-vinyl bridging to the adjacent aryl carbon except for the fluoro substituent (50% ortho, 50% meta). This regioselectivity is explained by Houk and Paquette, using a simple MO model taking into account the polarization of frontier orbitals caused by donor or acceptor substituents. Weak donors show very low regio-selectivity, since these groups cause only small polarization of the occupied orbitals.

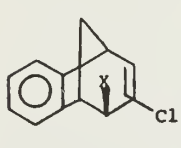


12

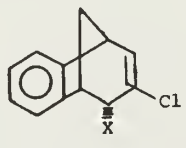
R = $COCH_3$, CN, NO_2, $CO_2C_2H_5$ $\xrightarrow[\text{sen.}]{h\nu}$ 13 (4)

R = OCH_3, NH_2, F $\xrightarrow[\text{sen.}]{h\nu}$ 14 (5)

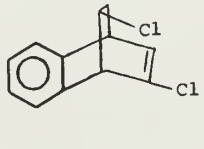
Direct irradiation of rigid bridged compound 15a at 254 nm in acetonitrile gave a mixture of 15a, 16a and the Wagner-Meerwein rearrange-arrangement isomer 17. Treating this mixture with water gave, besides those three compounds, a substantial amount of 15d. A mechanism involving a carboca-tion intermediate was proposed by Cristol.[24] Carbocation formation in



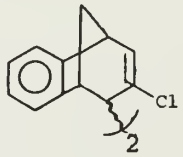
15 a: X = Cl
b: X = OM_s
c: X = C_6H_{11}
d: X = $NHCOCH_3$



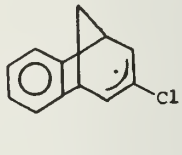
16 a: X = Cl
b: X = OM_s



17

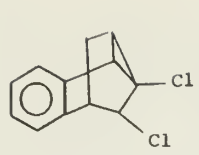


18

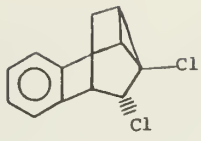


ε

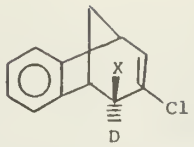
photochemically induced (or photo-sensitized) rearrangements and solvolyses has been reported[25] in other systems. Irradiation of 15a in cyclohexane gave only 15c and 18, from homolysis to ε and a chlorine atom. Triplet-sensitized reaction of 15a is different from the direct irradiation, leading to the di-π-methane rearrangement product 19, rather than the Wagner-Meerwein product. The di-π-methane rearrangement was stereospecific; thus, 15a



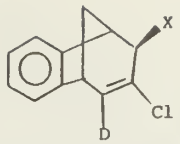
19



20

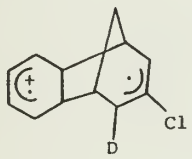


21 a: X = OMs
b: X = $NHCOCH_3$

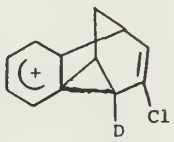


22 a: X = OMs
b: X = $NHCOCH_3$

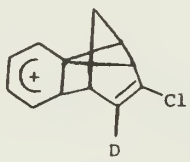
and 16a gave 19 and 20, respectively. Labeling experiments[26] have shown that the recovered 21a has no contamination of 22a. The photosolvolysis product comprised a mixture of 60% 21b and 40% 22b and the photoisomerized and rearranged methanesulfonates had less deuterium mixing. Results from irradiation of 22a were similar to those from 21a. The cation biradical d would be formed, which could decay to e and f by electron pairing to allow for deuterium scrambling. It is proposed[27] that the excited aromatic ring decays by intramolecular electron transfer to a carbon-chlorine bond to form the zwitterion diradical, which can return to the original compound, to an allylic isomer, or to the Wagner-Meerwein or other isomers, or undergo dissociation leading to photolysis. The homobenzyl allylic epimers 15a/16a and 15b/16b showed[24,26] little stereochemical requirement for photoreactivity or in product formation, a result rationalized by interaction between the allylic double bond (π or π^*) and C-Cl or C-O (σ or σ^*) orbitals. A stereochemical requirement for intramolecular electron transfer from the π, π^* excited state of the aromatic ring to the lobe of the C-Cl σ^* orbital was observed[28] in photolysis of 17 and 23. Compound 17, with chlorine anti to the benzene ring chromophore is photoactive and the migration of the syn chloroethenyl group occurs in modest preference to that of the anti benzo ring, while 23 is relatively photo-inert.



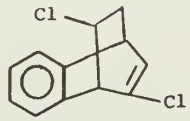
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e

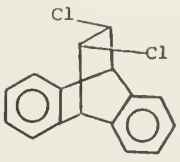


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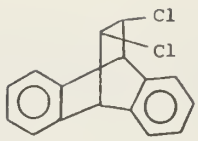


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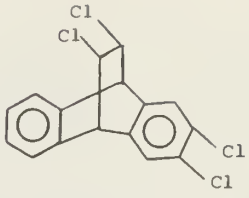
The homobenzylic systems[27e] 24-27 do show a stereochemical requirement for photoactivity and preferences for pathways. Irradiation of 24 in acetic acid gave the rearranged compounds 28a and 28b in 75% yield, while compounds 29a and 29b were produced in about 25% yield. Irradiation of 25 gave the same products, but in a reverse ratio. Photolysis of compound 26, with an anti dichlorobenzo group, gave solvolysis and photo Wagner-Meerwein rearrangement, whereas the syn compound 27 did not react. Stereochemical requirements are also seen in the photoreactions of 30a, 30b, 31a and 31b. These photoreactions require that β-carbon-chlorine or β-carbon-oxygen bond be positioned anti to the excited aromatic ring and that the major migrating ring be syn to the C-Cl or C-O bond rather than anti, as seen[29] in ground-state solvolysis. Morrison and Miller[30] have observed a similarly large preference for anti activation in benzo-2-norbornenyl systems.



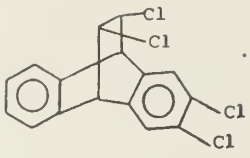
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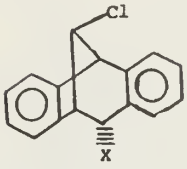
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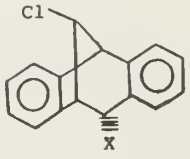
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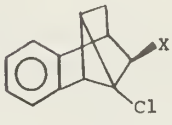
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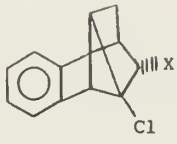
28 a: X = Cl
b: X = OAc



29 a: X = Cl
b: X = OAc

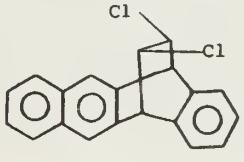


30 a: X = Cl
b: X = OMs

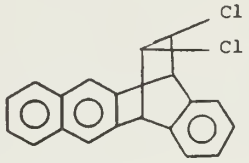


31 a: X = Cl
b: X = OMs

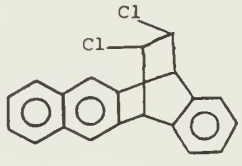
Further studies to understand the driving forces for the presumed electron transfer and for the competitive syn vs. anti bond migrations have been performed.[31] Irradiation of the naphthobenzo systems 32-34 or the veratro-benzo systems 35-37 gave a mixture of four products which result from electron transfer of the excited naphtho or veratro ring to



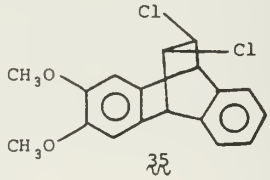
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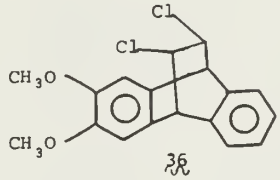
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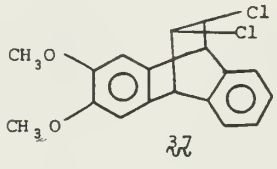
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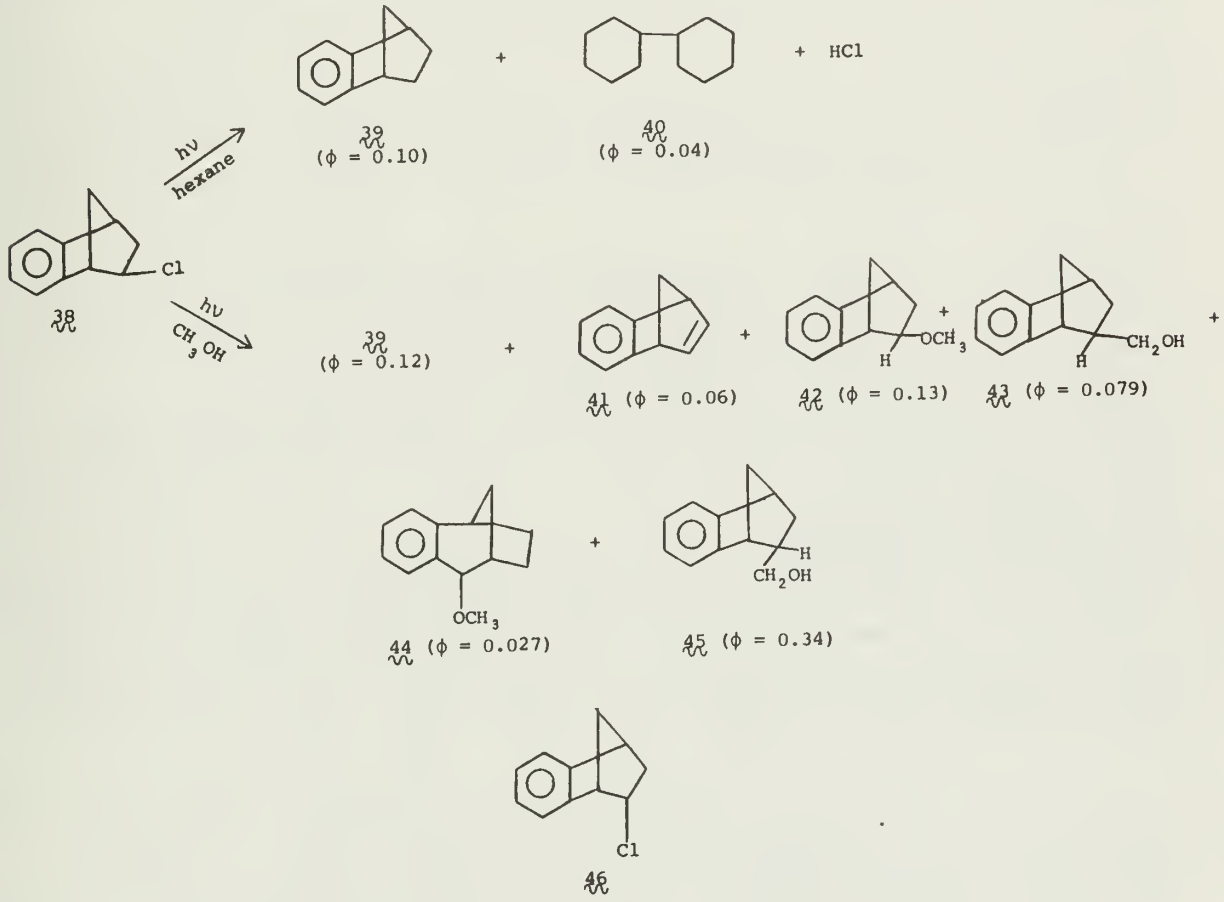


37

both the syn and anti carbon-chlorine bonds. Existence of an energy barrier[31] for electron transfer from the π^* orbital to the σ^* orbital (or to a combination π^* σ^* orbital) is found in the Weller equation[32] (Equation 6), in which ΔG is the free-energy change associated with the formation of radical cation-radical anion pairs by an electron transfer process, $E_{ox}(D/D^+)$ is the oxidation potential of the unexcited donor, $E_{red}(A/A^-)$ is the reduction potential of the acceptor, $^1E_{O-O}$ is the singlet excitation energy of the donor, N is Avogadro's number, e is the charge on the electron, ε is the effective dielectric constant of the medium separating the ions, and γ is the distance between the ions. The barrier is greater in the syn than in the anti case and this difference in barrier height might decrease or become less significant as the electron transfers become more exergonic (or less endergonic).

$$\Delta G = E_{ox}\,(D/D^+) - E_{red}\,(A/A^-) - {}^1E_{O-O}\,(D) - Ne^2/\varepsilon\gamma \qquad (6)$$

Morrison and coworkers[33] have reported the photophysical and photochemical properties of 2-benzonorbornenyl derivatives. Irradiation of 38 in hexane produces 39 and 40, which are derived from free radical precursors. Irradiation of 38 in methanol gives ionic products (e.g., 42, 44). Less than 2% deuterium incorporation is obtained in 39 when 38 is irradiated in basic CH_3OD. This intramolecular activation of the remote functionality by the aryl chromophore is strongly stereoelectronically controlled,[32,34] in that the reaction rate of 38 is 733 times faster than that of 46. The primary photoproducts from 38 are principally derived from the singlet excited state, which is confirmed by xenon perturbation, photosensitization, and fluorescence studies. The singlet-derived "hot" carbocations derived from both heterolysis and radical pair electron transfer have been supported[33] by solvent effect experiments. The process of electron transfer from the aryl π, π^* excited state to the C-Cl σ^* orbital is favored ($\Delta G_{et} = -12$ kcal/mole), as estimated by the Weller equation.[32]



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ETHYLENE BIOSYNTHESIS IN HIGHER PLANTS

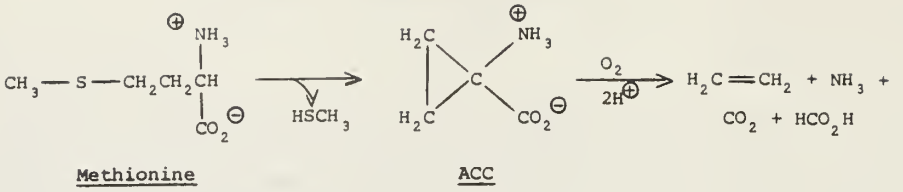
Reported by Jon Denissen April 30, 1984

Ethylene, a natural plant product, is one of the simplest organic compounds which is biologically active in trace amounts. Observations on the effects of ethylene on plant growth were first recorded in 1858, in descriptions of the behavior of plants exposed to illuminating gas.[1] In 1901, the study of the unusual growth pattern of etiolated pea seedlings raised in laboratory air contaminated with illuminating gas revealed that ethylene was the biologically active component of the gas.[2] The seedlings displayed subapical stem thickening, elongation rate depression, and horizontal nutation of the stem when exposed to ethylene, either pure or in the gas mixture. These and numerous other changes in the growth of plant tissues had hardly received attention when they were quickly overshadowed by the discovery that ethylene is the plant hormone responsible for fruit ripening.[3] Effort was diverted to this commercially important aspect of ethylene action and by 1935 it was established that ethylene is produced autocatalytically just in advance of fruit ripening.[4] Work in the 1960's showed ethylene production to be induced by plant auxins and the enzyme system required was shown to be constitutive in most higher plants. Regulation by ethylene was found to extend to the stages of flower formation, sex expression, flower fading, and fruit growth, in addition to fruit ripening.

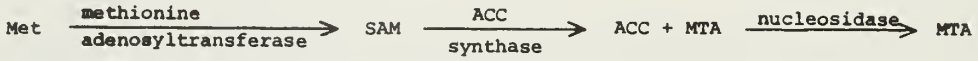
It is now generally believed that methionine serves as the biological precursor of ethylene in all higher plant tissues. It was first suggested as a possible precursor of ethylene by Lieberman *et al.*[5] as it was rapidly converted to ethylene in a model system containing copper ion and ascorbic acid. Burg and Clagett[6] showed conversion of methionine to ethylene to be the major pathway of methionine metabolism in several plant tissues. Moreover, incubation of L-[U-^{14}C]Methionine, DL-[1-^{14}C]methionine, DL-[2,^{14}C]-methionine, and L-[^{35}S]methionine with various plant tissues indicated that ethylene arises exclusively from C-3 and C-4 of methionine, while C-1 is lost as carbon dioxide, C-2 is converted to formate, and the methylthio group is retained in the tissue. However, until recently, the pathway from methionine to ethylene had remained obscure. Several new investigations have identified the intermediates in the biosynthetic pathway to ethylene and numerous mechanistic proposals have been put forth to explain the enzymatic conversions involved.

Methionine → SAM → ACC

In 1957, Burroughs[7] isolated a previously unknown amino acid, 1-aminocyclopropane-1-carboxylic acid (ACC), from the juice of perry pears. The metabolic significance of this amino acid was not investigated. However, it was noted that ACC appeared only during the last three to four weeks of ripening on the tree. The importance of ACC was not realized until 1979, when Lürssen[8] and Adams and Yang[9] independently showed ACC to be a key intermediate in ethylene biosynthesis. Lürssen incubated soybean leaves with ACC and observed a 100-fold increase in ethylene evolution, while incubation in nitrogen gave no ethylene. Similarly, Adams and Yang incubated apple slices with L-[U-^{14}C]methionine in a nitrogen atmosphere to find that ACC accumulated in the fruit tissue. No ethylene was produced. Therefore, it appeared that methionine was metabolized to ACC, which, in turn, was converted to ethylene only in the presence of oxygen.



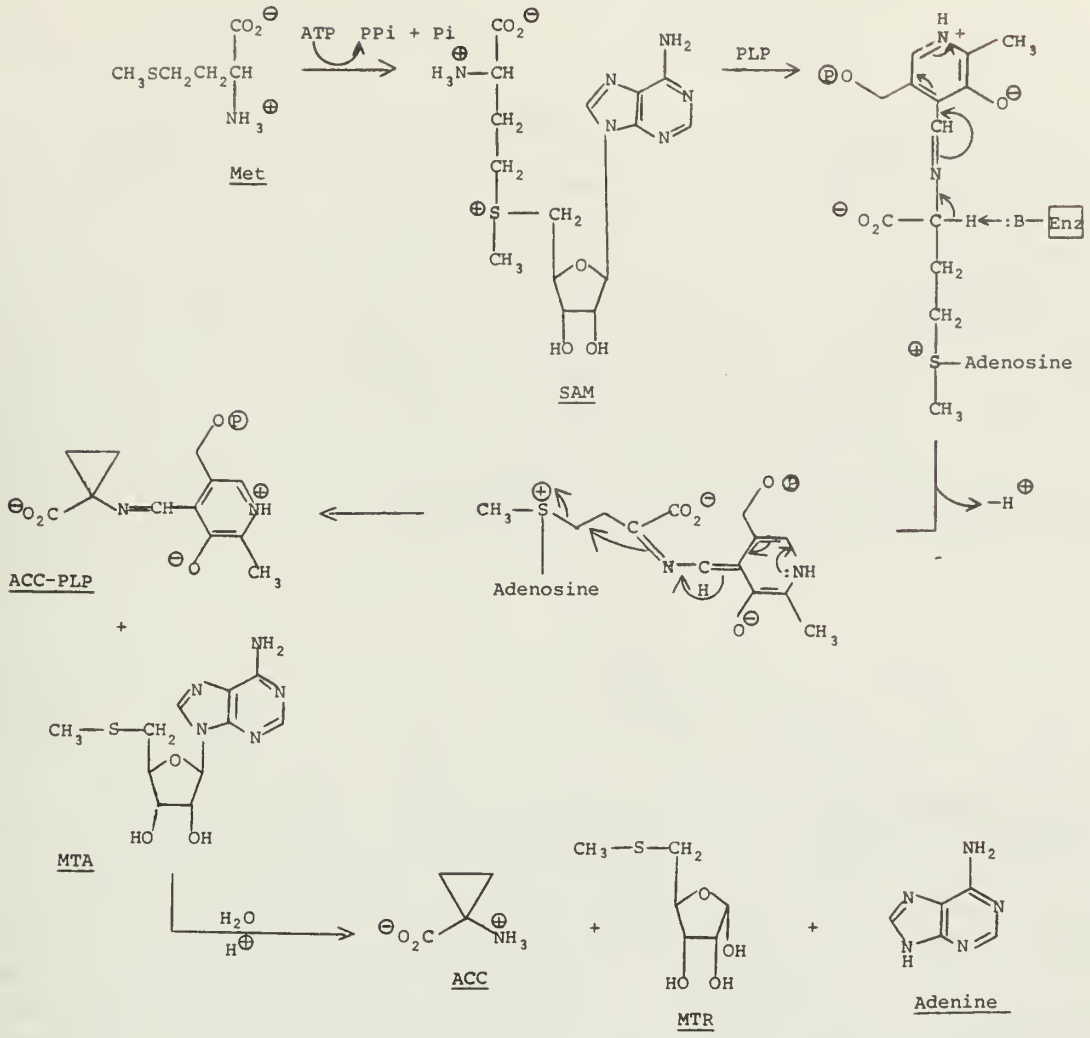
What are the intermediates in the biosynthesis of ACC from methionine? Based upon the fact that dinitrophenol, an uncoupler of oxidative phosphorylation, inhibited ethylene biosynthesis, Burg[10] proposed S-adensylmethionine (SAM) as a possible intermediate. This product of ATP and methionine coupling was shown to be formed in plants from [U-^{14}C]methionine.[6] The hypothesis was confirmed in 1977 by Adams and Yang.[11] When [methyl-^{14}C]- or [^{35}S]methionine was fed to ripening apples, radioactive 5'-S-methyl-5'-thioadensoine (MTA), the expected fragment nucleoside of SAM, and a large amount of 5-S-methyl-5-thioribose (MTR) were produced. The MTR was considered to arise from rapid hydrolysis of MTA. In 1979, Konze and Kende[12] prepared a cell-free extract containing methionine adenosyltransferase enzyme which converted methionine to SAM *in vitro*. ACC synthase, found to convert SAM to ACC and MTA, was isolated in a cell-free extract from tomatoes that some year by Yu *et al*.[13] A nucleosidase present in the extract hydrolyzed MTA to MTR and adenine. The following pathway emerged from this information:



Lürssen proposed a mechanism for the fragmentation of SAM to ACC and MTA involving coenzyme A and pyridoxal phosphate (PLP), yet provided no evidence for the involvement of either cofactor.[8] Adams and Yang, however, were able to implicate pyridoxal phosphate as an enzyme-linked mediator of this conversion.[9] They noted that aminoethoxyvinylglycine (AVG), a potent pyridoxal phosphate inhibitor, caused SAM to accumulate during methionine incubation, with no ACC or MTA formation observed. Structurally unrelated PLP inhibitors such as aminooxyacetate were also shown to have the same effect. Therefore, ACC synthase must be a pyridoxal phosphate enzyme. Of course, final proof requires isolation of pure ACC synthase, but Adams and Yang[9] did propose a reasonable mechanism for the conversion of methionine to ACC (Scheme I). Methionine is first activated by ATP to produce SAM, which then reacts with PLP to form a Schiff's base. If is well established that pyridoxal enzymes are capable of catalyzing the elimination of γ-substituents, β-hydrogens, and α-hydrogens of amino acids. However, the elimination of the α-hydrogen of SAM, accompanied by the γ-substituent (MTA), to give a cyclopropane ring represented a novel enzymic reation.

As early as 1972, Bauer and Yang,[14] noting the naturally low levels of methionine in apple tissue, proposed that the sulfur of methionine must be recycled to provide more methionine for continued ethylene production. In a dual-labeling experiment, Adams and Yang[11] incubated [methyl-^{3}H]- and [^{35}S]MTA having the ratio $^{3}H/^{35}S$ = 6.5 and isolated [methyl-^{3}H]- and [^{35}S]-methionine from the plant tissue. A ratio $^{3}H/^{35}S$ = 5.9 showed that the methylthio group of MTA nad MTR is transferred as a unit for incorporation into methionine. They proposed transfer of the group to an unknown 4-carbon receptor, perhaps homoserine. In 1980, Shapiro and Schlenk[15] identified the ribose portion of MTR as the source of the four additional carbons

Scheme I

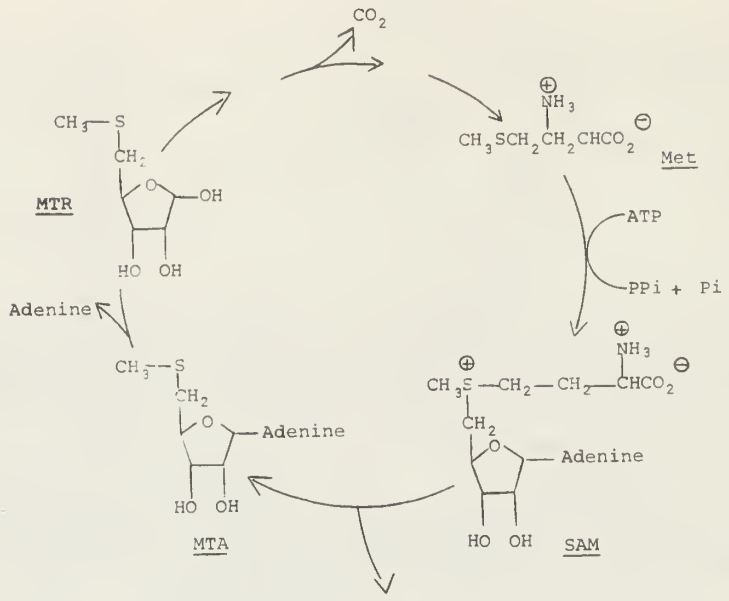


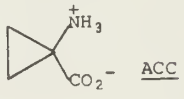
needed for methionine. 5'-methylthio-[U-^{14}C]adenosine (MTA) was incubated with the yeast Candida utilis and the resulting radioactive S-adenosyl-methionine was isolated. Complete hydrolysis of SAM to homoserine, adenine, and methylthioribose revealed almost all radioactivity to be located in adenine and homoserine, the hydrolysis product of methionine. The ribose portion contained almost no radioactivity. Yung et al.[16] incubated methyl-thio[U-^{14}C]ribose with apple slices to obtain ^{14}C-methionine and $^{14}CO_2$. A dual-label experiment using [methyl-^{3}H]MTR and [ribose-U-^{14}C]MTR with a ratio $^{3}H/\ ^{14}C$ = 1.10 gave methionine having a ratio $^{3}H/^{14}C$ = 1.35. Taking into account the loss of one carbon from ribose to the 2-aminobutyrate skeleton of methionine, a value of 1.37 (1.10 x 5/4) was expected. Therefore the ribose portion of ATP is used to recycle methionine. Ribose for ATP regeneration must come from other biosynthetic pathways. A general reaction scheme can be drawn as shown in Scheme II; however, no mechanistic proposals concerning the conversion of MTR to methionine have been made to date.

ACC Deaminase

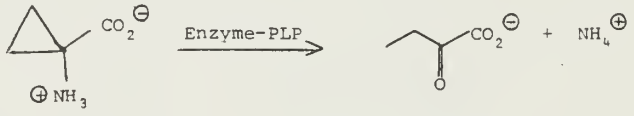
In 1978, Honma and Shimomura[17] isolated an enzyme in highly purified form from Pseudomonas soil bacteria which catalyzed the concomitant deamination and cyclopropane ring opening of ACC to yield α-ketobutyrate and ammonia both in vivo and in vitro. The enzyme required a cyclopropane moiety within the substrate for activity, and did not require oxygen. A UV maximum at 420 nm. and inhibition by carbonyl reagents indicated a

Scheme II

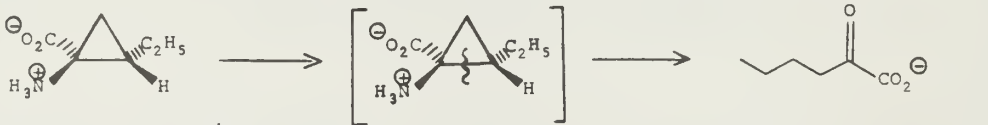




pyridoxal phosphate prosthetic group firmly bound to the enzyme. The ring opening was regarded as a γ-elimination by the deaminase, but ACC lacks the required α-hydrogen usually found in amino acid γ-eliminations. Therefore, it may be viewed as an intramolecular γ-elimination followed by azaallylic isomerization and hydrolysis. This bacterial ACC deaminase is clearly analogous to the reverse reaction of ACC synthase which converts SAM to ACC and MTA via PLP-mediated γ-elimination. Since examination of the biotransformation from ACC may yield vital insight into the biotransformation by which ACC is formed, this deaminase warranted further study in relation to the overall scheme of ethylene biosynthesis.



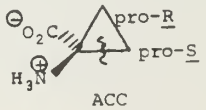
Honma et al.[18] synthesized racemic coronamic acid and incubated it with the deaminase. Only (+) - (1S,2S)-coronamic acid was processed by the enzyme. Furthermore, only L-amino acids were found to provide significant enzyme inhibition. Thus, the enzyme was stereoselective, catalyzing cleavage of the cyclopropane ring at the bond corresponding to an L-amino acid side chain. Accordingly, the pro-S methylene group



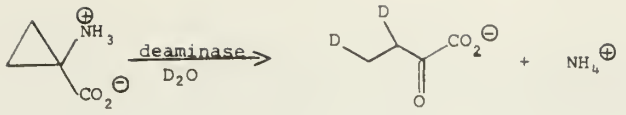
L-(1S,2S)-coronamic acid

α-keto-n-caproic acid

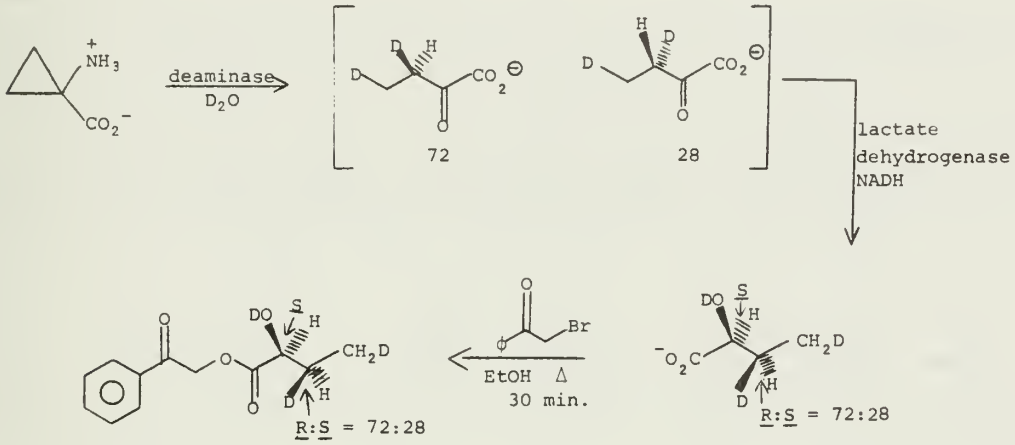
of ACC would be expected to interact with the enzyme active site providing bond cleavage between the pro-S methylene and the α-carbon.



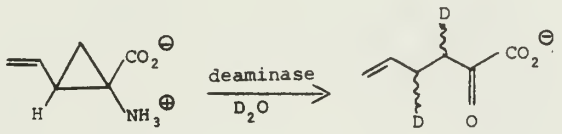
ACC



In an effort to further elucidate the route of cyclopropane ring cleavage, Walsh[19] incubated ACC with deaminase in 99% deuterium oxide and monitored deuterium incorporation by 250-MHz ^1H NMR spectroscopy. After 27.4 hr, complete substrate conversion was achieved and integration revealed introduction of one solvent deuterium at the C-4 methyl and one at the C-3 methylene of the α-ketobutyrate product. ACC, ACC deaminase, NADH, lactate dehydrogenase, and deuterated buffer were then incubated for 24 hr. The (2S)-2-hydroxy[3,4-$^2H_2$]butyrate formed was isolated as its phenacyl ester. The lactate dehydrogenase/NADH system provided in situ reduction of α-ketobutyrate to (2S)-2-hydroxybutyrate. When compared to the spectrum of the phenacyl ester of (2S)-2-hydroxy[3S-^{2}H)butyrate (prepared from a coupled D-threonine/D-serine dehydratase and lactate dehydrogenase/NADH system), the 250-MHz ^1H NMR spectrum of the ACC-derived phenacylester showed that deuterium was introduced by the enzyme at C-3 in a stereochemical preference of approximately 72:28 : R:S.

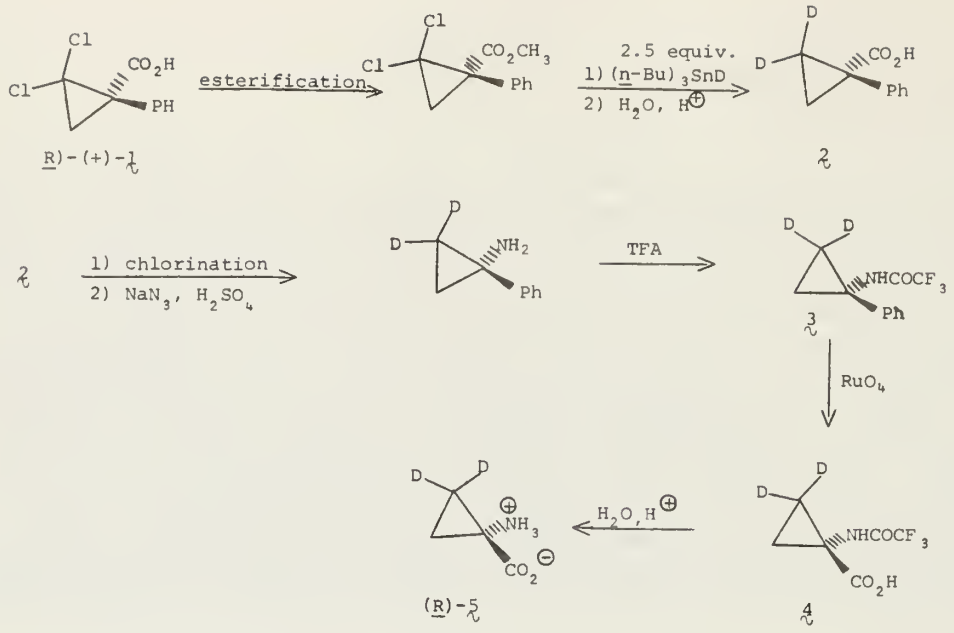


Walsh also studied 2-vinyl-ACC as substrate. Incubation with deaminase yielded only 2-keto-5-hexanoate as product detected by its 250-MHz ^1H NMR spectrum. Incubation in deuterium oxide similarly gave 2-keto-[3,4-$^2H_2$]-5-hexenoate. This provides additional support for single detuerium incorporation at C-3 and C-4 and for Honma's hypothesis of pro-S methylene interaction with the enzyme active site. Hill, Argoni, and Walsh[20] unequivocally proved this pro-S preference using dideuterated ACC substrates prepared by two independent routes.

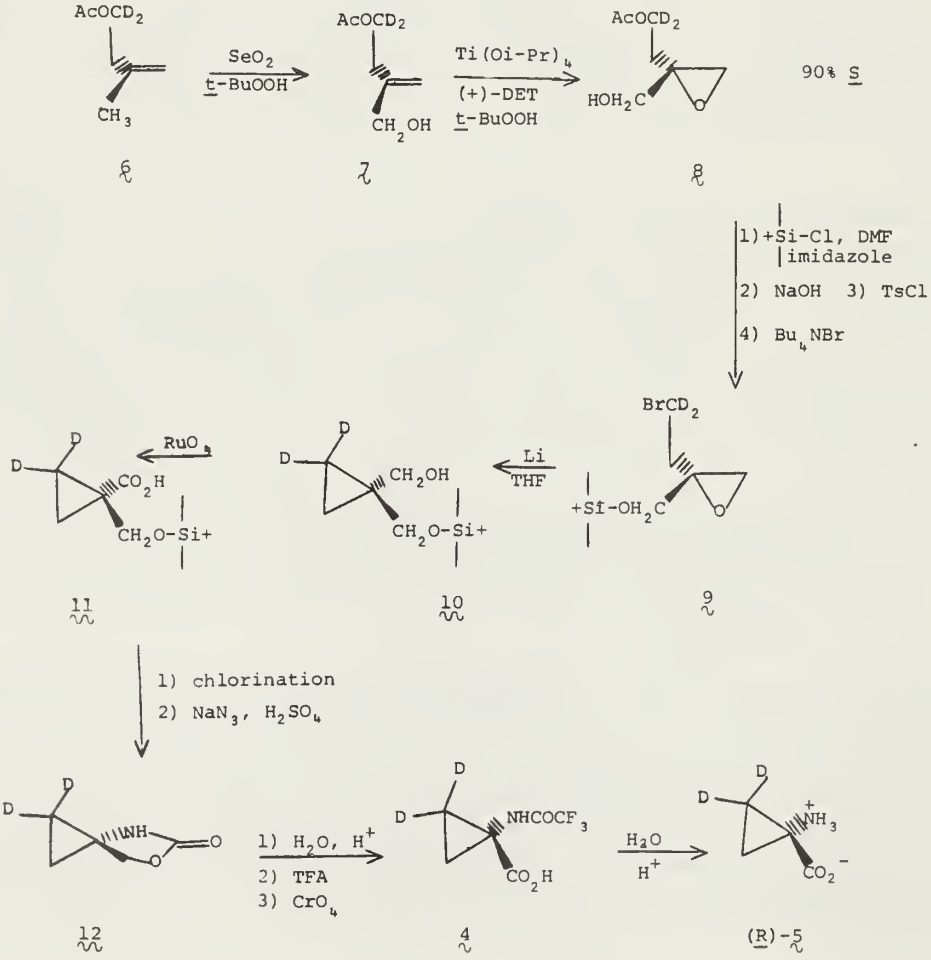


1S,2R and 1R,2S mixture

Hill's synthesis began with 2,2-dichloro-1-phenylcyclopropanecarboxylic acid (1). The (+) isomer was resolved as the α-methylbenzylamine and configurationally assigned as R. After conversion to the methyl ester, reducation with tri-n-butyltin deuteride and hydrolysis, the deuterated acid 2 was obtained. Curtius rearrangement of 2 led to the amine, purified as the crystalline trifluoroacetamide 3. Oxidation of 3 with ruthenium oxide gave acid 4, which was hydrolyzed to (R)-[2,2-$^2H_2$]ACC (5). Similarly, (S)-[2,2-$^2H_2$]ACC was prepared from (-) - 1.

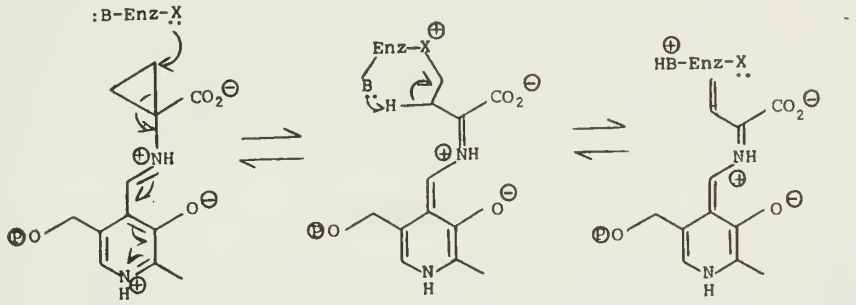


In Arigoni's synthesis, acetate 6 was oxidized by selenium dioxide and tert-butyl hydroperoxide to alcohol 7. Sharpless epoxidation gave the S epoxide 8, which was converted to the tert-butyldimethylsilyl ether and then to the bromide 9. Treatment with lithium gave the cyclopropane derivative 10, which was oxidized with ruthenium oxide to acid 11. Curtius rearrangement of 11 provided the oxazolidone 12, which upon hydrolysis, trifluoroacetylation, and chromic acid oxidation gave the amide 4. Hydrolysis yielded (R)-(-)-ACC 5. The S isomer of 5 was similarly produced using (-)-(diethyl)-tartrate.

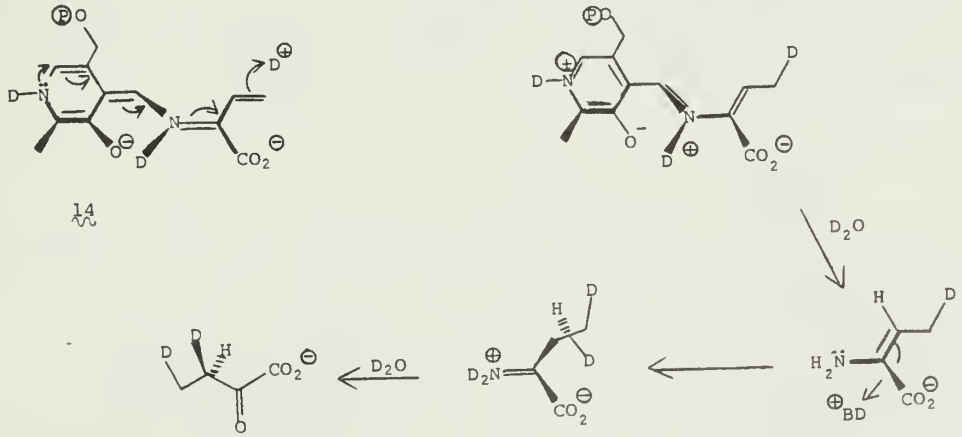


Enzymatic deamination was carried out with both (R)- and (S)-[2,2-$^2H_2$]ACC and was coupled to *in situ* reduction with lactate dehydrogenase/NADH. The resulting (2S)-2-hydroxybutyric acids were converted to the phenacyl esters and analyzed by 250-MHz ^1H NMR spectroscopy. ACC deaminase differentiated sharply between enantiotopic methylene groups of the substrates. The S dideuterated ACC yields product exclusively deuterated in the methyl group, while R dideutero-ACC gave α-ketobutyrate product labeled only at C-3. Thus, the methyl group has its specific origin in the pro-S methylene of the substrate, as predicted.

Walsh[19] has proposed a mechanism for the ring opening process and subsequent α-ketobutyrate production based upon a nucleophilic addition/elimination route. Fragmentation is achieved by attack of an active-site nucleophile at the pro-S methylene carbon of ACC to generate a p-quinoidal PLP-stabilized anion (13). Abstraction of one of the now acidic β hydrogens could give γ elimination of the enzyme moiety added initially, resulting in the fully conjugated vinylglycine-PLP α-anion (14). After 14 is produced, sequential γ-then β-reprotonation steps occur that incorporate one hydrogen (or deuterium) atom at each of carbons 4 and 3 of α-ketobutyrate. The reprotonation at C-3 probably occurs on free aminocrotonate still within the enzyme active site, explaining the 72:28 : R:S ratio observed for ACC incubation in deuterium oxide. This hypothesis is supported by the observa-



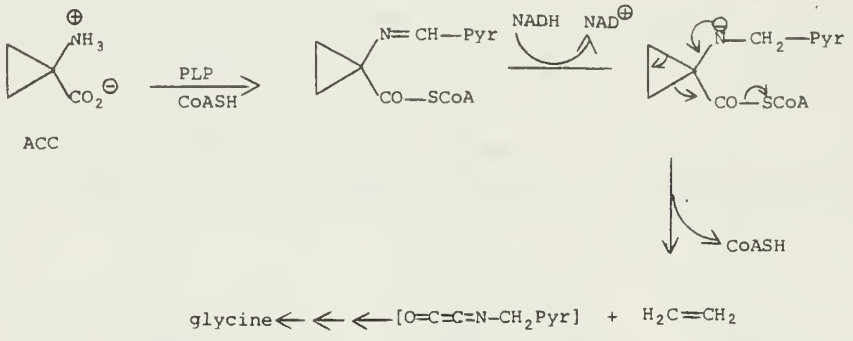
tion of a 56:44 : S:R distribution of deuterium label at C-3 of the phenacyl ester products of Hill, Arigoni, and Walsh's dideuterated ACC incubations. The deuterium removed from (R)-[$^2H_2$]ACC (5) in the formation of the vinylglycyl-PLP imine intermediate (13) must be shielded in the enzyme active site for return to C-3 in a subsequent step. However, it is not certain whether this return is stereorandom or favors return to give the R C-3 product.



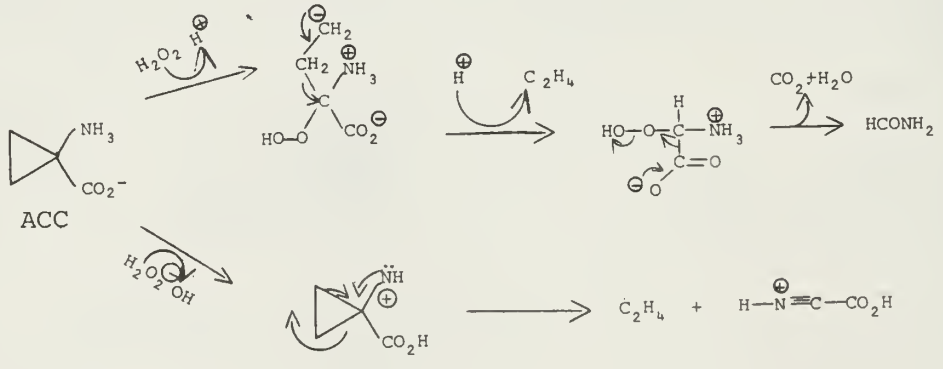
ACC → Ethylene

Although the enzyme system catalyzing the conversion of ACC to ethylene appears to be constitutive in most plant tissues, an active cell-free extract has yet to be isolated. The characteristics of in vivo conversion suggest that the exzyme is membrane associated, labile, and easily disrupted by various treatments. Information from in vivo systems also shows the enzyme to be oxygen dependent and inhibited by cobalt chloride, temperatures above 35°C, red light, free radical inhibitors, and copper chelators.[21]

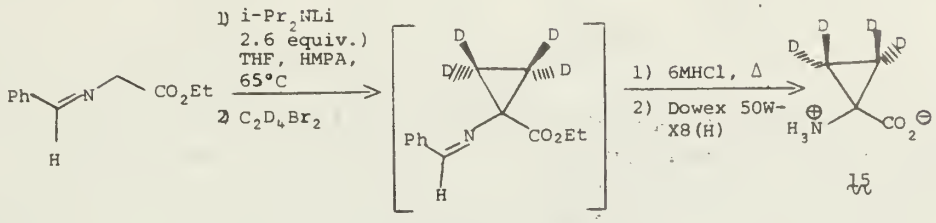
Early hypotheses of the mechanistic nature of this conversion were advanced by Lürssen[8] and Yang.[9] Lürssen suggested the formation of a Schiff's base between PLP and ACC, activated by coenzyme A, which also provides a good leaving group. A reduction stepwith NADH gives an intermediate which rapidly falls apart, liberating ethylene, coenzyme A, and a ketenimine of glyoxal. Driving force for this fragmentation would be loss of ring strain and gain in entropy. Recent work,[21] however, has shown that PLP inhibitors do not inhibit ethylene production and no evidence has been found to indicate the presence of coenzyme A or glyoxal derivatives in in vivo systems.



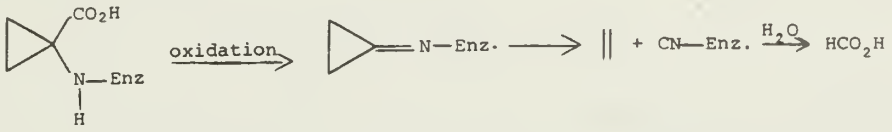
Yang propsoed the nucleophilic opening of the cyclopropane ring at the fully substituted carbon of ACC by hydrogen peroxide. Hydrogen peroxide liberates ethylene from ACC in several non-biochemical model systems; however, Konzé[22] added hydrogen peroxide to an ethylene-forming homogenate and observed no catalytic effect. Yang later proposed[23] oxidation of ACC by hydrogen peroxide to yield a nitrenium ion, which fragments to ethylene and cyanoformate conjugate acid.



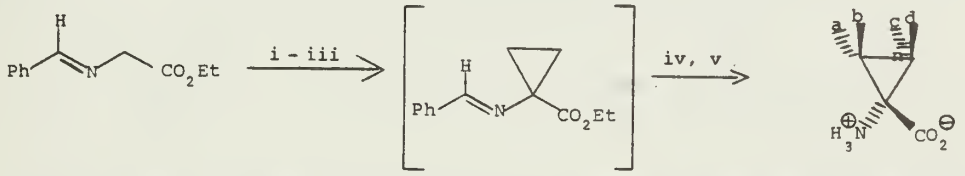
Baldwin has recently synthesized [2,2,3,3-$^2H_4$]ACC (15) by a double nucleophilic displacement reaction in 28% yield.[24] Incubation of this



substrate with apple slices gave [$^2H_4$]ethylene without loss of deuterium, leading Baldwin to propose a mechanistic scheme involving covalent bonding between ACC and the enzyme, oxidative decarboxylation to a cyclopropanone imine, and extrusion of ethylene. An isonitrile would result, which is then hydrolyzed to formate.



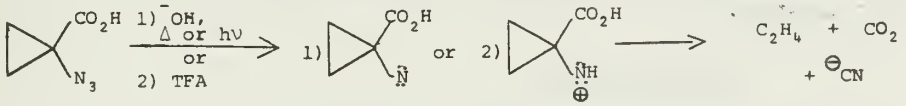
Baldwin has also synthesized stereospecifically labeled ACC.[25] Trans- and cis-dideuterioethylenes were brominated to yield meso- and (±)-dibromoethylenes, respectively. Reaction with the lithio derivative of benzylidene glycine ethyl ester gave cis-[$^2H_2$]ACC (as a 1:1 mixture of 16 and 17) and (±)-trans-[$^2H_2$]ACC (18 and 19), respectively. Incubation of these substrates gave 1:1 mixtures of cis- and trans-dideuterio-ethylene in all cases, implying a complete lack of stereospecificity in the biosynthetic ethylene pathway.



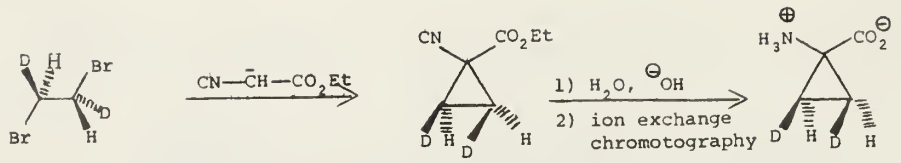
i, i-Pr$_2$NLi(1.25 equiv.), THF, -78 → -60°C;
ii, dideuterated ethylene dibromide;
iii, i-Pr$_2$NLi (1.25 equiv.); iv, 6MHCl,↑↓;
v, Dowex 50W-X8(H), Dowex 1 X 8 -400 (Acetate).

(16) a=c=^{1}H; b=d=^{2}H
(17) a=c=^{2}H; b=d=^{1}H
(18) a=d=^{1}H; b=c=^{2}H
(19) a=d=^{2}H; b=c=^{1}H

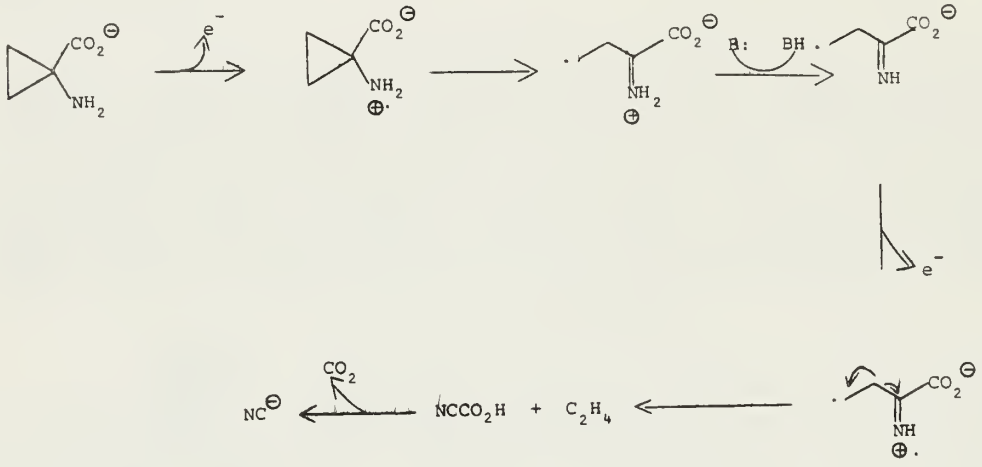
In order to evaluate the merits of the above hypotheses, Pirrung investigated the decomposition of 1-azidocyclopropanecarboxylic acid thermally, photochemically, and under acid catalysis.[26] In all cases, ethylene, carbon dioxide, and cyanide ion were produced. Pirrung postulated the intermediacy of either a nitrenium ion (as in Yang's proposal) or a nitrene for the biosynthetic conversion of ACC to ethylene. He went on the prepare cis-ACC-



d_2 from meso-1,2-dibromo-1,2-dideuterioethane in 36% yield.[27] Incubation with apple and canteloupe discs gave 1:1 mixtures of cis- and trans-dideuterioethylenes by IR, confirming Baldwin's results. Pirrung believed this result implied a nonconcerted stepwise oxidation mechanism, thus disfavoring a nitrene or nitrenium ion intermediate. Focusing on the remaining possibility, a radical cation intermediate, Pirrung examined an electrochemical oxidation model. ACC was examined by cyclic voltammetry, where current of increasing



potential was passed through an ACC solution until oxidation occurred. Ethylene product was obtained; furthermore, cyanide ion was detected in molar amounts equal to that of ethylene. Similar oxidation of ACC-d_2 gave stereochemically scrambled dideuterioethylene, just as in the *in vivo* system. Pirrung postulated that ACC is converted to ethylene by means of an amine radical cation, generated from two one-electron oxidation steps and a deprotonation step. Subsequent β-fragmentation gives ethylene and cyanoformic acid, while decarboxylation of the acid yields carbon dioxide, as observed in the natural system, and cyanide. The loss of stereochemistry is due to free rotation of the C-2, C-3 bond in the radical or cation intermediates.



Since his model system produced cyanide ion, Pirrung argued that cyanide, not formate, was produced *in vivo* as the metabolic product of C-2 of methionine. Recent unpulished work by Pirrung, in which he treated apple tissue with ^{13}C-labeled sodium cyanide or ACC labeled with ^{13}C at C-1 of the cyclopropane ring, has shown the label to appear at the γ-carboxyl group of asparagine. Thus, cyanide is, indeed, the natural biosynthetic conversion product and is quite rapidly incorporated into asparagine.

Current research is concentrating on the questions of enzyme isolation and characterization, requlation mechanisms, and inhibition of this ethylene biosynthetic system.

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ANTINEOPLASTIC AGENTS FROM MARINE ORGANISMS

Reported by Tom Holt

May 3, 1984

The experiments of a Chinese physician around 2700 B. C. mark the first recorded use of marine natural products for the treatment of cancer.[1] In modern times, studies of the antitumor activity of sea cucumber extracts by Nigrelli in 1952 initiated interest in the sea as a potential source of anticancer drugs.[2,3] Interest developed slowly until the National Cancer Institute (NCI), 15 years later, began systematic screening.[4] Since then, several pharmaceutical companies and research groups have shown interest in searching for new antineoplastic compounds from marine organisms. To date, only one compound resulting from these investigations has progressed to clinical trials.[5] Nevertheless, a number of quite active marine species have been identified and several antineoplastic compounds have been characterized. In the search for novel antineoplastic agents, the natural products chemist is concerned with (1) screening crude extracts, (2) bioassay-directed isolation, and (3) structural determination of the active compounds.

Screens

In screening crude extracts for antineoplastic activity, an unusual event (an active compound) must be detected at trace levels (ca. 1 ng/mL) in complex matrices. The screen should demonstrate adequate sensitivity, accept large numbers of samples with reasonable speed, and correlate well with in vivo activity. Normally, a crude extract is screened initially for cytotoxicity against an in vitro tumor cell line, such as the KB (human nasopharyngeal carcinoma) or the P388 or L1210 (murine leukemia) cell lines. Cytotoxic extracts are then screened for in vivo activity (typically against P388 leukemia).[6] More selective in vitro screens, such as the inhibition of the synchronous cell division of the fertilized sea urchin egg,[7] have occasionally been used.[4,8,9,10] Initial screens which can be performed in the field are especially desirable.[11]

Pure compounds with demonstrated in vivo activity against P388 leukemia may be sent to the NCI for further testing against a panel of in vivo tumors (five mouse tumor lines and three human tumor lines carried in athymic mice). Novel compounds with a sufficiently broad spectrum of activity in the tumor panel are candidates for development into drugs for clinical trials.[4]

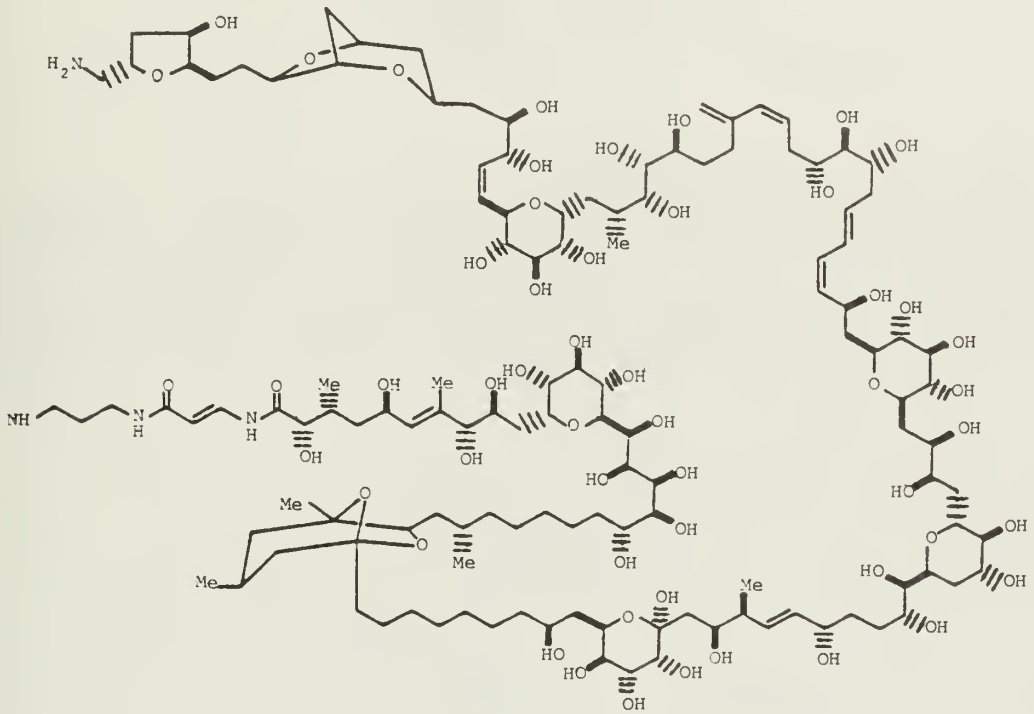
Isolation

Once the antineoplastic activity of an extract is confirmed by in vivo data, the isolation of the active component may be followed by in vitro assays. Ideally, after each purification step, the cytotoxic component is checked for in vivo antineoplastic activity.[12] In sample-limited cases, this is not always possible, but if in vivo activity is not checked, the investigator may ultimately isolate and identify cytotoxic compounds (showing in vitro activity) that are not responsible for the in vivo activity of the original extract. The antinoplastic agent may possess other, more easily assayed, bioactivities (e.g., antibacterial activity), and these may be exploited to follow the isolation. Bioautography on a normal cell line (CV-1 monkey kidney cells) also has been used to direct the isolation.[13]

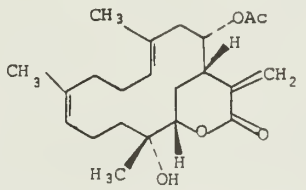
Structures

Within the past 15 years, numerous compounds have been isolated from *in vivo*-active extracts. Although many of these compounds are cytotoxic against tumor cell lines, only six have demonstrated activity against *in vivo* tumors. Five phyla are represented by these compounds.

Coelenterata. The exceedingly toxic compound palytoxin (1) (LD_{50} = 25 ng/kg in rabbit) completely cures Ehrlich ascites carcinoma in mice, but shown only marginal *in vivo* activity against P388 leukemia (T/C^a = 132).[14] The toxin is found in Hawaiian and Japanese coelenterates belonging to the genus *Palythoa* but may be actually produced by symbiotic bacteria. Another coelenterate natural product, crassin acetate (2), is isolated from Caribbean gorgonians of the genus *Pseudoplexaura*.[15] This cembrane diterpene also exhibits only marginal *in vivo* activity (P388: T/C = 130).



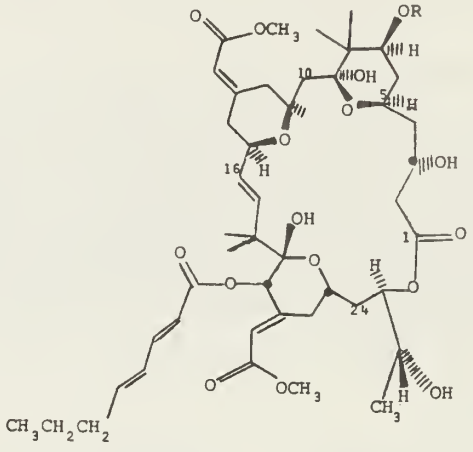
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2

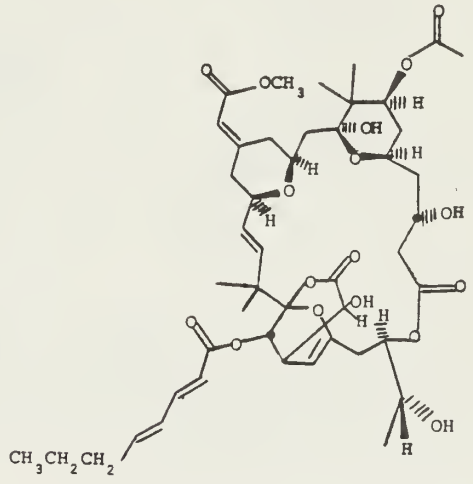
[a] "T/C" = Ratio of average lifetime of treated mice to average lifetime of control mice x 100.

Bryoza. The bryostatins (3, 4, 5), recently isolated from Bugula neritina, are novel macrolides showing significant activity against P388 leukemia (T/C = 152-196).[16] In testing against the NCI tumor panel, however, bryostatin 1 (3), the most active bryostatin, has failed to show a broad spectrum of activity.[17]



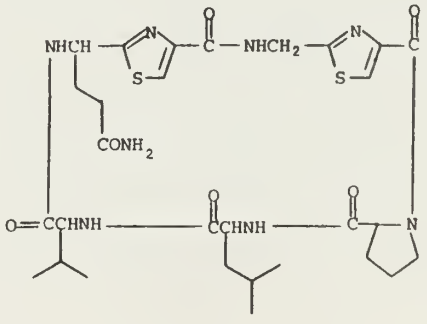
3, R = $COCH_3$

4, R = H



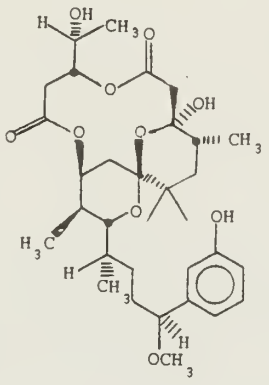
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Mollusca. The dolastatins derive from the Indian ocean sea hare, Dolabella auricularia.[18] The cyclic peptide, dolastatin 3 (whose structure was originally assigned as 6), shows strong in vitro activity in the P388 system (ED_{50} = 1 x 10^{-7} μs/mL). Dolastatin 1, of as yet unknown structure, is quite active against B16 melanoma in mice (T/C = 240).



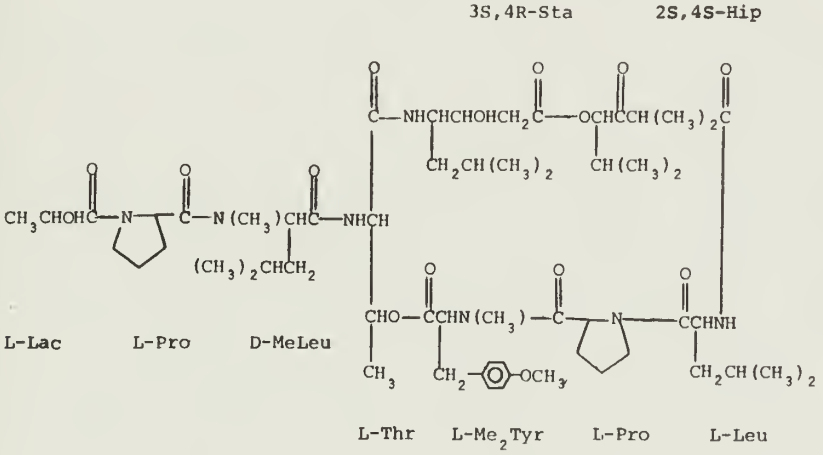
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Cyanophyta. Debromoaplysiatoxin (7), isolated from the Hawaiian blue-green alga Lyngbya gracilis, shows significant activity against P388 leukemia (T/C = 167).[12,19] The compound is also found in sea hares of the genus Stylocheilus. Evidence suggests that the latter organism obtains the compound from its algal diet.



7

Chordata. The most promising structurally characterized antineoplastic marine natural product to date has been didemnin B (8), isolated from a Caribbean tunicate of the genus Tridemnum.[20] This cyclic depsipeptide shows remarkable activity against P388 and B16 tumors (T/C = 199 and 160, respectively) and is currently in NCI phase I clinical trials. Didemnin B is also a potent antiviral[21] and immunosuppressive[22] agent.



8

Of the more than one million species of marine invertebrates and 25,000 species of fishes, only some 0.06% have been assayed for antineoplastic activity by the NCI. Given the structural variety and novelty of the compounds isolated thus far, one can be certain that many more marine antineoplastic compounds await discovery.

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ORGANIC SEMINAR ABSTRACTS

1984-85, Semester I

University of Illinois

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SEMINAR TOPICS

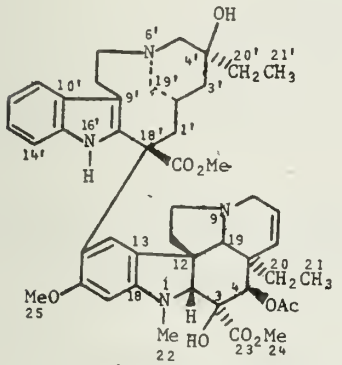
Semester I, 1984

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SYNTHETIC APPROACHES TO VINBLASTINE

Reported by Gary L. Clauson October 4, 1984

The periwinkle family, consisting of the two genera Catharanthus and Vinca, is a rich source of alkaloids,[1] among which is vinblastine (VLB, **1**[2]), a potent anti-tumor agent.[3] Since this bisindole alkaloid is present in the leaves of the source plant (the Madagascar periwinkle, Catharanthus roseus (Vinca rosea)) to an extent of only 0.05%,[4] a number of attempts have been made to synthesize **1**, with varying success.



1

The first synthetic methods, using the chloroindolenine approach on analogs of the VLB monomers,[5] failed to give the natural S configuration at C-18', critical for biological activity. Potier and co-workers,[6] using a modified Polonovski reaction (believed to be biomimetic), were able to obtain a mixture of R and S anhydrovinblastine, an air-sensitive compound found later to be present in the plant.[7] Atta-Ur-Rahman et al. were the first to synthesize VLB itself by this method, starting with vindoline and 4'-acetoxy-3',4'-dihydrocatharanthine N-oxide;[8] Mangeney et al.[9] were able to synthesize VLB in 30% yield from 3',4'-dihydrocatharanthine N-oxide. This approach also affords VLB derivatives from substituted monomers and mixed bisindole analogs from bases other than vindoline.[5d,7]

Some biological methods have recently been used to produce VLB. Kutney and coworkers[10] used plant tissue cultures and cell-free extracts to obtain VLB (and a number of other Catharanthus alkaloids) in small quantities; a Japanese patent[11] shows that 10.2 μg VLB per g of dry tissue can be obtained from such cultures. McLauchlan et al.[12] have used a different cell line to produce a cell-free extract that catalyzes the conversion of anhydrovinblastine into VLB.

Improvement in these synthetic and biological methods, along with refinement of the biological activity of VLB by judicious modification, are being actively pursued.

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FORMAL THREE-CARBON PLUS TWO-CARBON CYCLOADDITION REACTIONS

Reported by Douglas A. Burg October 15, 1984

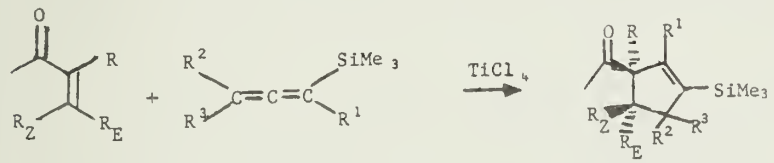
Reactions in which multiple bonds are formed regio- and stereospecifically are of unusual synthetic value. The [π4s + π2s] cycloaddition process of the Diels-Alder reaction is widely used to form a six-membered carbocyclic ring in a four-carbon plus two-carbon fashion. In contrast, the three-carbon plus two-carbon cycloadditions are not as well known nor as well characterized. Such a route to five-membered carbocycles would be very useful, since cyclopentenes are a part of many natural products such as prostaglandins, steroids, and hirsutenes. Recently, there has been considerable interest and some success in the development and characterization of three-plus-two cycloadditions to give cyclopentanes. The reaction between an allyl anion and an olefin as in Scheme I is one example of this type of reaction.

Trimethylsilyl Cyclopentene Annelation

The (trimethylsilyl)cyclopentene annelation[1,2] is a one step reaction that involves the addition of (trimethylsilyl)allenes (2) to electron deficient alkenes (allenophiles) (1) in the presence of titanium tetrachloride to give cyclopentenes (3). The reaction is regiospecific and stereoselective and generates highly substituted cyclopentenes. The cycloaddition also has a strong preference for suprafacial addition of the allene to the allenophile. Thus, the allenophile stereochemistry is usually preserved, allowing for the stereocontrolled synthesis of a variety of products. For cyclic allenophiles this produces cis-fused products. In Table I are some examples of this cycloaddition. Note the regiospecific and suprafacial addition.

Scheme I





1 2 3

a) R^1 = Me, R^2 = R^3 = H

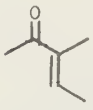
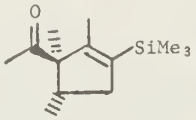
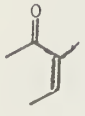
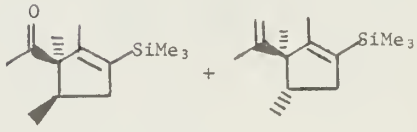
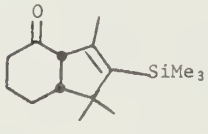
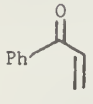
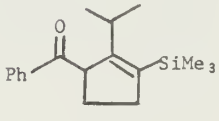
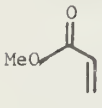
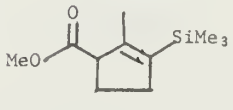
b) R^1 = R^2 = R^3 = Me

c) R^1 = i-Pr, R^2 = R^3 = H

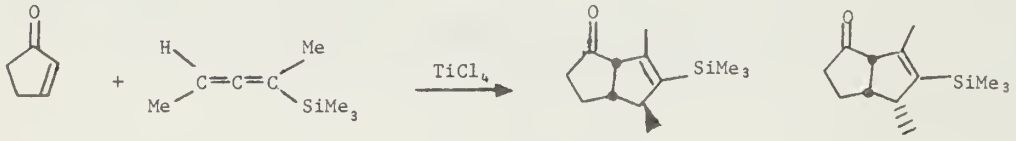
Some stereoselectivity is also seen when a third stereocenter is added by employing a C_3 monosubstituted allene, such as 4, which when reacted with cyclopentenone gives a 3:1 mixture of the bicyclic

Table 1.

Trimethylsilyl cyclopentene annelations

Allenophile	Allene	Products	% Yield
	2a		71
	2a	 13-19:1	68
	2b		63
	2c		69-73
	2a		49

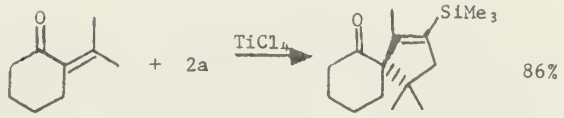
products 5 and 6. Spiro-fused systems (e.g. 8) are generated by the reaction of an α-methylenic ketone (7) with a (trimethylsilyl)allene. The reaction of the acetylenic allenophile 9 successively with two



4 5 6

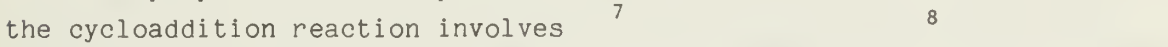
68% (5:6 = 3:1)

equivalents of allene generates the bicyclo[3.3.0]octadiene system **10.**

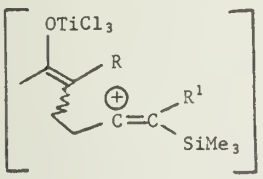


7 8

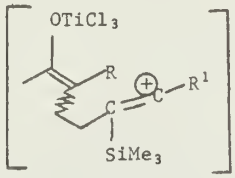
The proposed reaction path for the cycloaddition reaction involves complexation of the enone and the titanium tetrachloride to produce an alkoxy allylic carbonium ion. Regiospecific electrophilic substitution at C_3 of the (trimethylsilyl)-allene forms a vinyl cation (**11**) which is stabilized by interaction with the adjacent carbon-silicon bond. This direct stabilization in the transition state cannot result from attack at C_1 of the allene since the carbon-silicon bond is coplanar with the allylic π bond. Since the carbon-silicon bond is orthogonal to the vinylic π system it can provide stabilization of C_3 electrophilic attack. The trimethylsilyl group then undergoes a 1,2-shift to afford an isomeric vinyl cation (**12**) which combines with the titanium enolate to produce the cyclopentene.



9 10



11

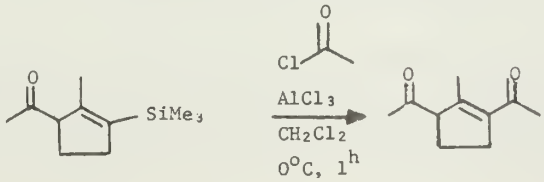


12

Poor yields (17-19%) are obtained for allene **2** when R^1=H. This is explained by the proposed reaction path since formation of the terminal vinyl cation (**12**) would be less favorable than the substituted vinyl cation **11.** The major product isolated in this case is an acetylene generated from desilylation of the more stable cation **11.**

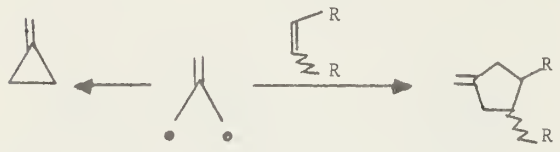
Desilylation of the (trimethylsilyl)cyclopentenes is accomplished by exposure to either potassium carbonate in methanol or a dilute solution of hydrofluoric acid in acetonitrile. These desilylation methods result in 96-64% yields with isomerization, when possible, to the α,β-unsaturated ketones. The vinylsilane functionality can be used for other transformations. Vinylsilanes are known to undergo regiospecific electrophilic substitution with many electrophilic species. Scheme II shows one example.

Scheme II



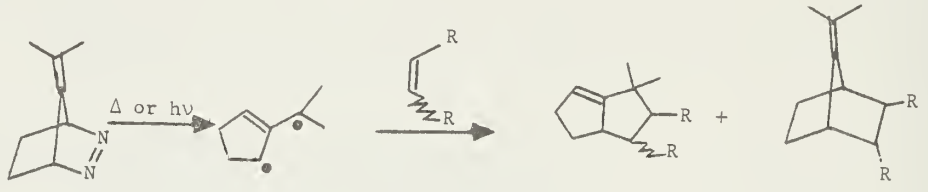
1,3-Diyl Trapping

The diradical (diyl) trimethylenemethane (TMM) (**13**) can be trapped with olefins to produce cyclopentane derivatives.[3-5] TMM itself has not been very useful in the trapping of olefins because of the competing side reaction of intramolecular closure to form methylenecyclopropane.



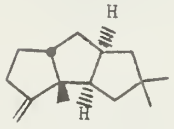
13

One method of preventing this side reaction is to join the methylene carbons of TMM with an ethano bridge. This imposes a strain barrier against ring closure and allows time for the diyl trapping reaction to compete. A bridged diyl (**15**) can be formed by the loss of nitrogen from compounds such as **14**. Trapping of the diyl leads to a fused product (**16**) and a bridged product (**17**). Formation of the fused product is favored when the olefin concentration is "high."[6] Conjugated olefins are the best trapping agents, and high yields of cycloadducts are observed with conjugated dienes, styrene, and α,β-unsaturated esters



14 15 16 17

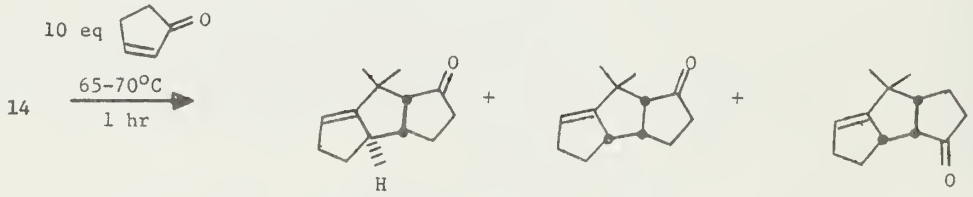
or nitriles. Reaction of the bridged diyl with cyclopentenones forms linearly fused tricyclopentanoid systems which are common to a number of natural products such as hirsutene (**18**).



18

While the reaction in Scheme III does show a slight regio- and stereoselectivity, the major product does not exhibit the desired cis,anti-fusion of most of the desired natural products as represented by **18**.

Scheme III

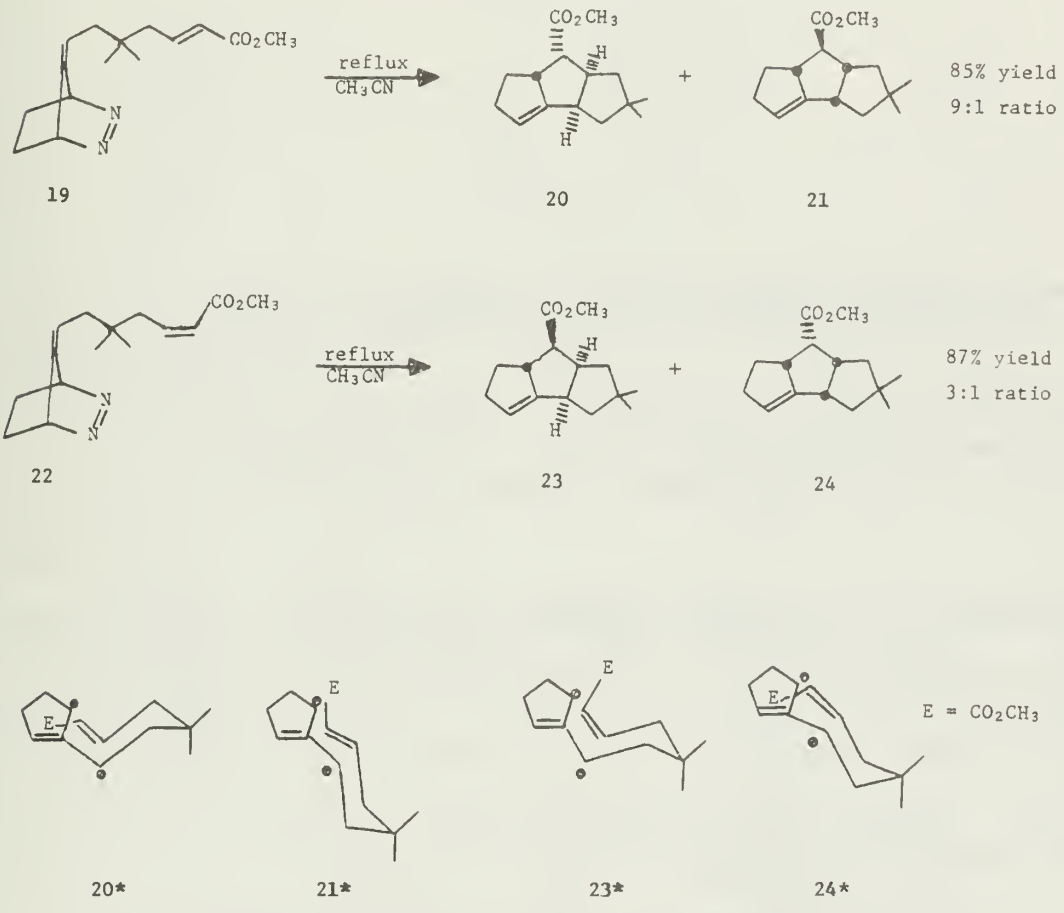


90-98% yield (1.3:1:3 ratio)

In order to provide better control of regio- and stereoselectivity, intramolecular diyl trapping reactions were tried. The desired regiochemistry and cis,anti stereochemistry of **20** was predominant in a 9:1 mixture as shown in the first reaction of Scheme IV. The

cycloaddition was attempted with both the E (**19**) and the Z (**22**) double-bond diylophile configurations. The reaction is stereospecific with respect to retention of olefin geometry and stereoselective with respect to the ring-fusion stereochemistry. The cis,anti-fusion is predominant (Scheme IV) regardless of the geometry about the olefin. The major products in both the E and Z olefin cases, **20** and **23** respectively, arise from the preferred extended pseudochair conformers **20*** and **23***. The reaction of the E olefin shows more stereoselectivity (9:1) than the Z olefin (3:1) because the transition state leading to **20**, **20***, benefits not only from a lower energy diyl conformation just as **23*** does but **20*** also benefits from an energy lowering secondary orbital interaction between the ester and the diyl ring.

Scheme IV

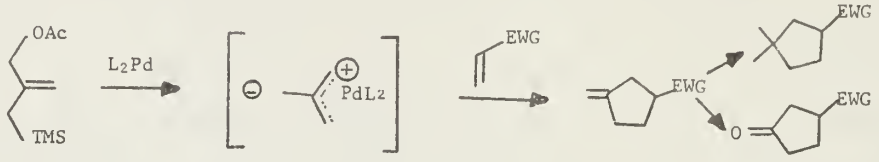


The tricyclopentanoid skeleton (**20**) was then transformed into the natural product d,l-hirsutene (**18**) in eleven steps in 6-9% yield.

TMM-Pd Complexes

TMM-Pd complexes are also very useful in three-carbon plus two-carbon cycloadditions.[8,9] This topic was covered in a recent

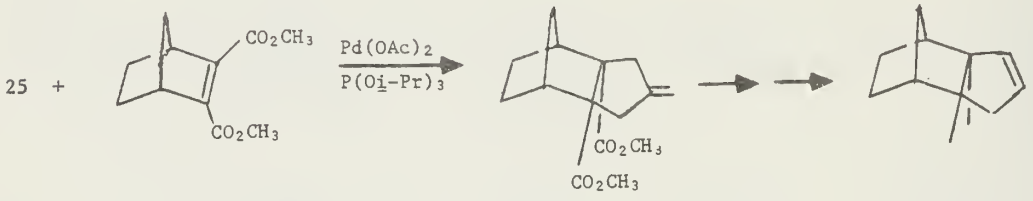
seminar[7] concerning π-allyl palladium complexes and therefore the reaction will be only briefly outlined. The TMM-Pd complex (**26**), which is generated from **25** by palladium-induced ionization followed by desilylation, reacts with an electron deficient olefin to yield a



25 26

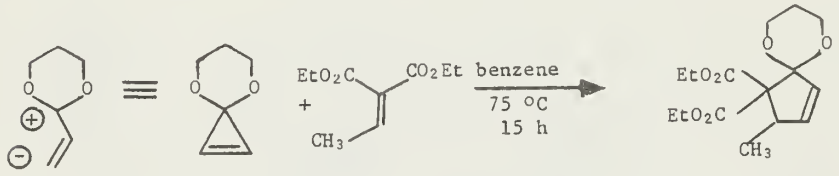
methylenecyclopentane system that can be functionalized further as desired. This method was used to synthesize (±)-albene[10] (Scheme V).

Scheme V



Formal 1,3-Dipolar Cycloaddition of Cyclopropenone Ketals

A preliminary study of formal 1,3-dipolar cycloaddition of cyclopropenone ketals has been reported.[11] The thermal reaction of the cyclopropenone ketal **28** with an electron-deficient olefin produces the cyclopentenone ketal **29** in 57% yield. This cyclopropenone serves as the synthon of the 1,3-dipole **27**. A necessary condition for this cycloaddition is the use of two electron-withdrawing groups on the olefin: esters, nitriles, or ketones. Examples of the reaction are shown in Table II. Note the regiospecificity of the reaction.

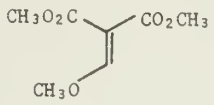
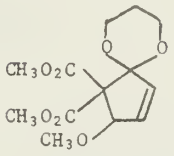
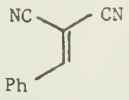
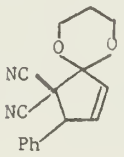
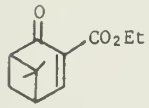
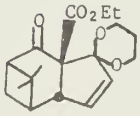
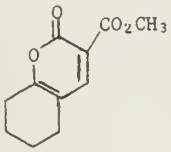
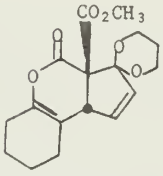


27 28 29

The proposed regiospecific reaction pathway involves initial nucleophilic attack of the cyclopropene on the electron-deficient olefinic bond, rearrangement of the resulting cyclopropyl cation, **30**, to

Table II

Reaction of cyclopropenone ketal 28 with electron-deficient olefins

Olefin	Product	% Yield
		84
		86
		45
		42

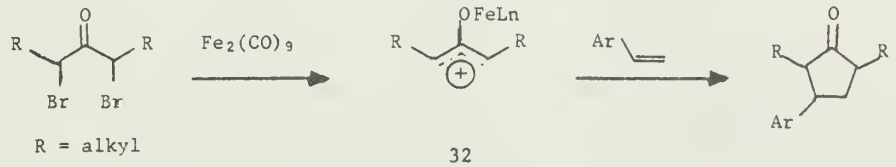
the allylic cation, **31**, and collapse of the dipole to produce the observed products.



30 31

[3+2] Cyclocoupling Reaction Between α,α'-Dibromo Ketones and Olefins

The reaction of α,α'-dibromo ketones with $Fe_2(CO)_9$ generates the 2-oxyallyl-Fe(II) species **32**, which can be trapped by aryl-substituted olefins to produce cyclopentanones.[12-15] The reaction is stereospecific

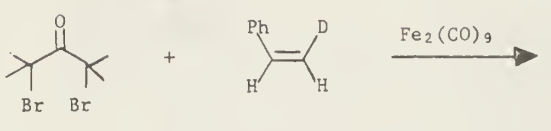


R = alkyl

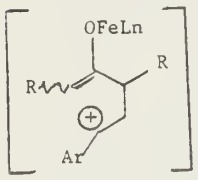
32

with respect to retention of the double-bond configuration. This is shown by reaction of the dibromide **33** with cis-β-deuteriostyrene to give cyclopentanone **34**. The concerted reaction of a $[2_\pi + 2_\pi]$ system such as

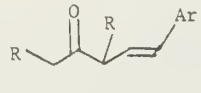
this is symmetry forbidden; accordingly, the mechanism is proposed to be stepwise. Open-chain byproducts, such as **36** also lend support to the stepwise reaction path since they can be formed from an intermediate such as **35** by loss of a proton. While one substituent α to the ketone was required for reaction to occur, the tertiary dibromo ketones were slow to react and formed a 1:1 mixture of cyclopentanone and alkylidenetetrahydrofuran derivatives **37**. Cyclopentenones can be synthesized by a similar method[16] employing secondary dibromo ketones and enamines. The reaction proceeds as before to give, for example, the β-morpholinocyclopentanone **38**. This product can then easily undergo deamination to yield the cyclopentenones. This reaction can be used to form a wide range of



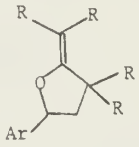
33 **34**



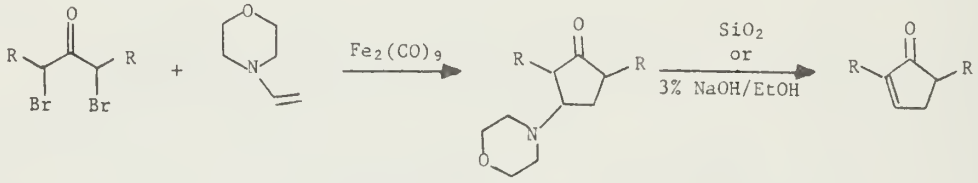
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36

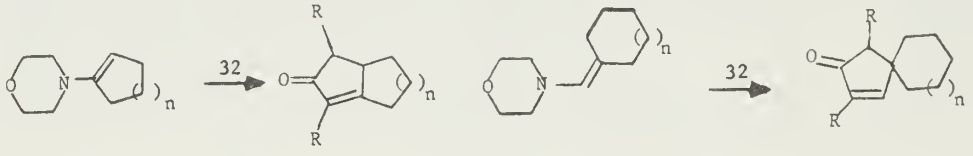


37



38

cyclopentenones. By using various substituted enamines such as **39** and **41**, bicyclo[n.3.0]alkenones (**40**) and spiro[4.n]alkenones (**42**) can be synthesized.

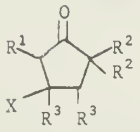


39 **40** **41** **42**

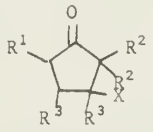
The aryl-substituted olefin and enamine cycloaddition reactions are regioselective and, depending on the substituents, sometimes regiospecific. When the aryl-substituted olefin is used as the trap for a phenyl-substituted α,α'-dibromo ketone, only one cyclic product (**43a**) is observed, as shown in Table III, entries 1 and 2. When R'=methyl, two cyclic products are formed, **43a** and **43b**, in a ratio of 6:94 (Table III, entry 3). The same general pattern holds when using the enamine as the trap; however, the reaction is less regioselective (Table III, entries 4,5, and 6).

Table III

Regioselectivity of the [3 + 2]cyclocoupling reaction between α,α'-dibromo ketones and olefins



43a

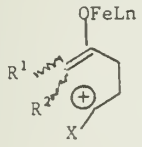


43b

Entry	a:b	% Yield	X	R^3	R^1	R^2
1	100:0	44	Ph	H	Ph	H
2	100:0	49	Ph	H	Ph	CH_3
3	6:94	31	Ph	H	CH_3	CH_3
4	76:24	22	$-N(CH_2CH_2)_2O$	$-CH_2(CH_2)_2CH_2-$	Ph	H
5	75:25	61	$-N(CH_2CH_2)_2O$	$-CH_2(CH_2)_2CH_2-$	Ph	CH_3
6	41:59	86	$-N(CH_2CH_2)_2O$	$-CH_2(CH_2)_2CH_2-$	CH_3	CH_3

The observed regioselectivity is best explained by the relative stability of the zwitterionic intermediate **35**. The enolate stability sequence shown in Scheme VI shows that formation of the more stable enolate leads to the more predominant regioisomer in Table III. The

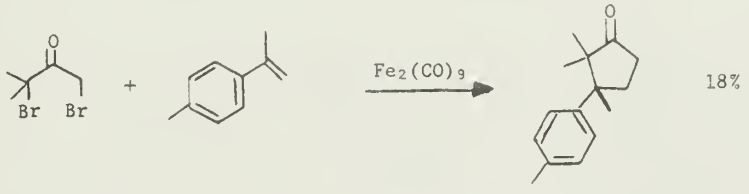
Scheme VI



X = Ph or $-N(CH_2CH_2)_2O$

R^1 = Ph, R^2 = H > R^1 = R^2 = CH_3 > R^1 = CH_3, R^2 = H > R^1 = R^2 = H

regioselectivity obtainable allows for a one-step synthesis of the cuparene-type terpene[18] **44**.



44

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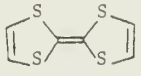
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PROPERTIES INFLUENCING THE ELECTRICAL CONDUCTIVITY OF CRYSTALLINE ORGANIC CHARGE TRANSFER COMPLEXES

Reported by Robert C. Hall October 18, 1984

Most crystalline organic compounds behave as electrical insulators. During recent years, however, a number of organic charge-transfer complexes have been prepared which exhibit metal-like conductivities in the solid state. These complexes consist mainly of closely stacked (3.2 - 3.6 Å apart) planar donor (D) and acceptor (A) molecules, with highly anisotropic electrical conductivity occurring along the stack axis. The most widely known conducting complex is TTF-TCNQ (Tetrathiafulvalene-7,7,8,8-Tetracyanoquinodimethane) (**1** and **2**) which



1



2

has shown room-temperature single crystal conductivities[1] as high as $\sigma = 10^3$, where $\sigma = \Omega^{-1}cm^{-1}$ (all σ values given are for room temperature). Conductivities for some non-organic compounds are compared to TCNQ complexes in Table I. These conductive complexes all exhibit two

Table I

Some conductivities of common materials

Material	σ(300 K)
Cu	6.4×10^5
InSb	3.5×10^2
n-Silicon	4×10^1
TCNQ Complexes	$1 - 10^3$
Anthracene	$< 10^{-14}$

important characteristics that distinguish them from the insulating complexes. One is that organic metals exist as segregated stacks of D and A molecules (...DDD//AAA...) in the crystal lattice rather than alternating (...DADADA...) stacks. The other important feature is that metallic complexes all have only a partial degree of electron transfer ρ resulting in "mixed valence," or partial oxidation of the D and partial reduction of the A molecules in the donor and acceptor stacks. For the chemist interested in preparing an organic complex with metal-like conductivity, control of these two properties would be necessary. The

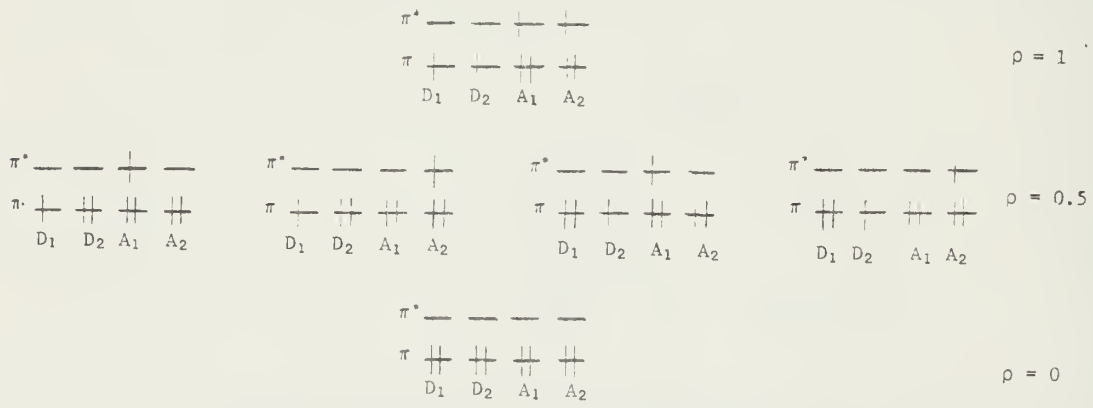
primary purpose of this review is to examine the factors influencing the mode of D-A stacking and the degree of electron transfer ρ.

Modes of DA Stacking

For a collection of n donor and n acceptor molecules $(DA)_n$, a certain amount of electron transfer from the donor's HOMO π orbitals to the acceptor's LUMO π* orbital can be represented by $(DA)_{n-i}(D^+A^-)_i$, with the degree of electron transfer ρ = i/n (i = 0,1,2,...n). A recent work by Shaik[2] has pointed out that the formation of mixed stacks of D and A molecules stabilizes the ground (ρ = 0) state whereas the aggregation of D and A molecules in segregated stacks will stabilize the excited states where 0 < ρ < 1. This rationalization can be most easily seen by looking at the smallest unit that can form segregated or mixed stacks in the crystal lattice, $(DA)_2$, consisting of two donor and two acceptor molecules. The set of possible configurations for the $(DA)_2$ unit consists of the ground state $(D_1^0D_2^0A_1^0A_2^0)$, four ρ = 0.5 configurations $(D_1^+D_2^0A_1^-A_2^0)$, $(D_1^+D_2^0A_1^0A_2^-)$, $(D_1^0D_2^+A_1^-A_2^0)$, and $D_1^0D_2^+A_1^0A_2^-$), and the ρ = 1 state $(D_1^+D_2^+A_1^-A_2^-)$. These configurations (shown in Figure 1) represent various wave functions which can interact

Figure 1

Configurations of $(DA)_2$



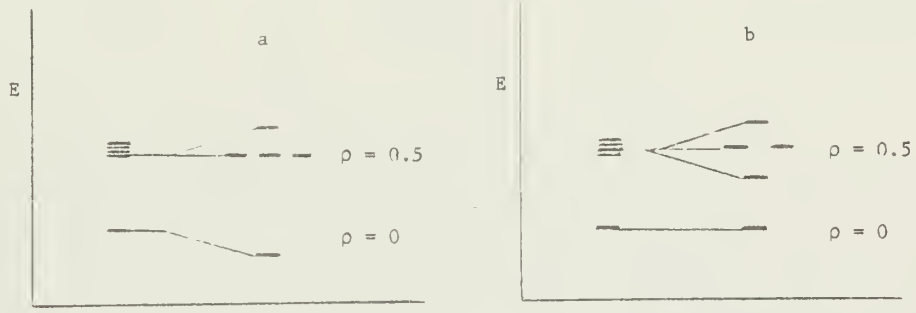
by a single electron shift. The ρ = 0 state interacts with the ρ = 0.5 state by an electron shift from the HOMO of the donor (π_D) to the LUMO of the acceptor (π^*_A), while the ρ = 0.5 configurations can interact amongst themselves by electron shifts from π_D to π_D and π^*_A to π^*_A. The resonance integrals for the interactions between these orbitals are represented by β_{DA}, β_{DD}, and β_{AA} respectively. Stabilization of the ρ = 0 and ρ = 0.5 configurations is shown in Figure 2. For a larger collection of D and A molecules $(DA)_n$, a large number of ρ values is

obtainable by varying the degree of electron transfer, with the largest number of β_{DD} and β_{AA} interactions possible for the $\rho = 0.5$ state.

Figure 2

a) Stabilization of $\rho = 0$ configuration by mixed stacking

b) Stabilization of $\rho = 0.5$ configuration by segregated stacking



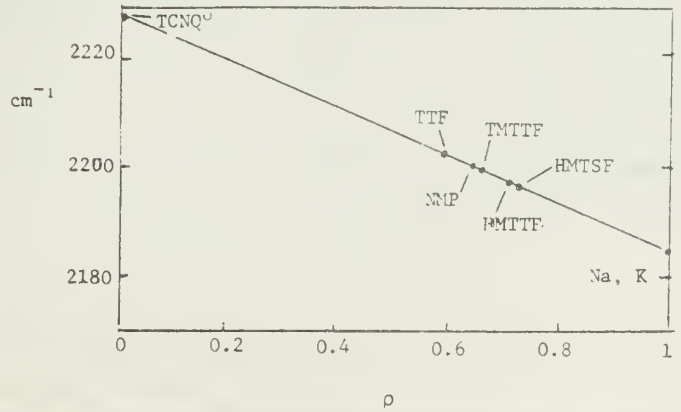
Degree of electron transfer

The degree of electron transfer ρ between the D and A molecules in an organic metal is primarily determined by the ionization potential of the donor I_D, and the electron affinity of the acceptor, A_A. Combinations of donor and acceptor molecules with moderate I_D and A_A values are more likely to form complexes having intermediate values of ρ and high conductivity (for TTF-TCNQ, $I_D - A_A \simeq 4$ eV).[2] Donors and acceptors that are too easily ionized will form ionic complexes (salts), while those that are difficult to ionize will form neutral ($\rho = 0$) complexes.

The value of ρ for TCNQ complexes can be most easily determined by IR spectroscopy.[3] The nitrile stretching frequency of TCNQ undergoes a linearly varying red shift upon increasing charge donation from donors of increasing strength. Neutral ($\rho = 0$) TCNQ shows a nitrile stretching frequency of 2227 cm^{-1} and fully ionic TCNQ (from $Na^+ TCNQ^-$), of 2183 cm^{-1}. The plot of ρ versus nitrile stretching frequency is shown in Figure 3.

Figure 3

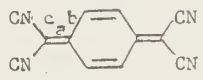
Nitrile stretching frequency (cm^{-1}) vs ρ for some D-TCNQ complexes



Bond lengths from crystal structures (if known accurately) have provided a simple way of estimating ρ.[4] Some of the bond lengths in TCNQ vary linearly with increasing ionization. Comparison of ρ obtained by both IR and bond length are given in Table II.

Table II

ρ from IR and bond length



a/(b + c)	Complex	ρ(IR)	ρ(b. l.)
0.476	TCNQ	0.0	0.0
0.486	$TMTSF^{\rho}$-TCNQ	0.65	0.42
0.488	TMPD-$(TCNQ)_2$		0.50
0.491	TTF-TCNQ	0.59	0.62
0.493	TMTTF-TCNQ	0.65	0.71
0.500	$TCNQ^-$	1.0	1.0

From I_D and A_A along with the Madelung binding energy, E_m, in equation (1), a value is obtained that reflects the relative value of ρ[5,6]. Since E_m is gained when a D-A pair forms an ionic crystal (salt), and a large $(I_D - A_A)$ favors a neutral lattice, cases with $E_B \simeq 0$ are characteristic for complexes where $0 < \rho < 1$ (E_B in equation (1) does not reflect a true binding energy for a D-A crystal, but is useful for telling if mixed valence exists for a D-A pair).

$$E_B = E_m + (I_D - A_A) \qquad (1)$$

The values of $E_m + (I_D - A_A)$ are given in Table III for some insulating and conducting complexes of TCNQ.

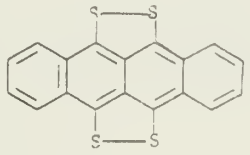
Table III

E_B for some TCNQ complexes

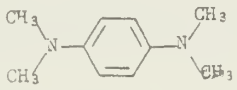
Complex	E_B(eV)	ρ	σ
Rb^+-$TCNQ^-$	-3.3	1.0	10^{-4}
Na^+-$TCNQ^-$	-3.0	1.0	10^{-4}
NMP-TCNQ	+0.5	0.63	10^2
TTF-TCNQ	+1.7	0.59	10^3

For several donors the electrochemical reduction potential has been used as an estimate of the relative ionization potential.[5,6] For the reaction $D^+ + e^- \rightarrow D^o$, a peak potential E_p (vs. SCE in CH_3CN, Pt electrode) in the range of -0.1 to +0.5 V is characteristic for donors forming complexes (with TCNQ) having only a partial degree of charge transfer and relatively high conductivity.

A partial degree of charge transfer can be obtained occasionally by forming a complex with a stoichiometry differing from the usual 1:1 ratio. A number of Donor-TCNQ complexes of 1:2 stoichiometry such as TTT (tetrathiatetracene)-TCNQ (3)[7] and TMPD (N,N,N',N'-tetramethyl-p-phenylenediamine)-TCNQ (4)[7,8] have much higher conductivity (as much as 10^2 times greater) than the corresponding 1:1



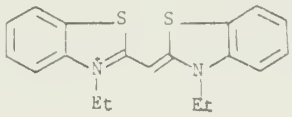
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complexes. In these cases the acceptor stack can never be more than one-half reduced when the donor is completely oxidized), resulting in mixed valence ($0 < \rho < 1$) and electrical conduction in the acceptor stack. The highly conductive series of salts $(TMTSF)_2 X$ (TMTSF = tetramethyltetraselenafulvalene **10**, X = ClO_4^-, ReO_4^-, PF_6^-, SbF_6^-, AsF_6^-, and TaF_6^-)[9] all have $\rho = 0.5$ for TMTSF due to D:A stoichiometry of 2:1.

Cases exist where complexes and salts have both segregated stacking and partial electron transfer but are electrical insulators. In most of these cases lack of electrical conductivity has been attributed to mismatched D-A sizes, with the smaller ions localizing charge on the nearest counterions. The 2:3 salt of Cs-TCNQ is an insulator[2,7,10] (σ 10^{-3}) even though $\rho = 0.67$ because the TCNQ stacks are distorted due to the presence of both $TCNQ^0$ and $TCNQ^-$.[8,9] Distortion of the TCNQ stacks also has occurred when donors much larger than TCNQ are used. The insulating 3,3-diethylthiacyanine-TCNQ complex (5) ($\sigma = 10^{-10}$) exists as stacks of dimers of D and A molecules.[10]



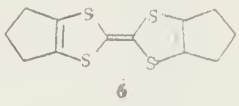
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Complexes with mismatched D and A sizes often result in formation of dimers or tetramers along the D and A stacks.

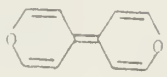
Extensive geometric rearrangement upon ionization may also present a barrier to delocalization[2] of the unpaired electrons in complexes with mixed valence and segregated stacks. Cases where the geometries of

neutral D and A differ greatly from D^+ and A^- are expected to have large-energy barriers to conduction.

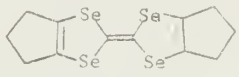
One way of overcoming barriers to delocalization is by increasing β_{DD} and β_{AA} by substituting larger heteroatoms. This heavy-atom effect on conductivity has been observed in HMTTF (Hexamethylenetetrathiafulvalene)-TCNQ (**6**) ($\sigma = 5 \times 10^2$) and its selenium analogue HMTSF-TCNQ (**7**) ($\sigma = 2 \times 10^3$)[7], and (pyranyl)pyran (**8**) (σ(powder) = 10^{-2}) and its sulfur analogue (**9**) (σ(powder) = 4).[11]



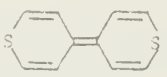
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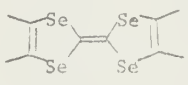


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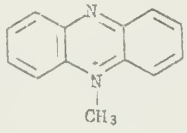


9

A question exists as to the thermodynamic stability of the segregated-stack organic metals relative to other ways of crystal packing.[2,7] As mentioned earlier, the segregated stack arrangement stabilizes an excited rather than the ground state. Intra-stack repulsions between like ions could be avoided by mixed-stacking. One may ask why the segregated stacking complexes exist at all when a presumably thermodynamically more stable mixed-stack isomer is possible. Evidence for the difference in thermodynamic stability of segregated and mixed stack isomers of the same D-A pair can be seen in the polymorphism of TMTSF (Tetramethyltetraselenafulvalene)-TCNQ (**10**) (σ (seg. stack isomer) = 8×10^2) [2,12,13] and NMP (N-Methylphenazine)-TCNQ (**11**) (σ(seg. stack isomer) = 10^2) [7,14].



10



11

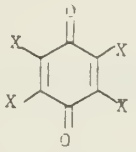
In both cases electrically conducting crystals were obtained by non-equilibrium crystallization. TMTSF-TCNQ and NMP-TCNQ crystals grown slowly from saturated solutions at room temperature gave non-conducting mixed-stack structures, while rapid cooling of hot saturated solutions yielded the segregated-stack conducting forms. To obtain the more conductive isomer for a given D-A pair, conditions of kinetic control in crystallization whould be used rather than thermodynamic control. For a given D-A pair, Shaik[2] estimated that for the value ($I_D - A_A$) $\simeq$ 4 eV,

the segregated and mixed stack isomers should be of comparable thermodynamic stability, and that for $(I_D - A_A) \geq 4$ eV, the conducting isomer is not the thermodynamically more stable isomer.

Another case where mixed- and segregated-stack polymorphism has been observed is with the TTF and TMTTF complexes with tetrahalobenzoquinones (**12**).[15] This has resulted in a new class of organic metals involving an organic acceptor other than TCNQ. Some powder conductivities for these complexes are given in Table IV.

Table IV

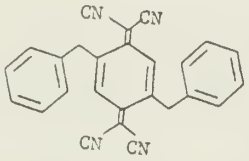
σ(powder) for some TTF and TMTTF complexes with (12)



12

σ(powder)	X = F	X = Cl	X = Br
TTF	10	8×10^{-4}	6×10^{-4}
TMTTF	7	20	1

Recently, an attempt has been made to enforce segregated stacking by placing both donor and acceptor on the same molecule. The molecule DBTCNQ (2,5-dibenzyl-7,7,8,8-tetracyanoquinodimethane) (**13**)[16] was



13

designed with the segregation of the stacks already "built in." The DBTCNQ, with D-A stoichimetry 2:1, shows crystal packing with segregated stacking of the acceptor portions of the molecule and a ρ value of 0.31. Perfect segregated stacking of both D and A portions is prevented by the orthogonality of the benzyl and TCNQ parts of the molecule.

Though such recent successes with organic metals as the $(TMTSF)_2$ X complexes[10] have occurred, organic complexes have some serious limitations in their usefulness as conductors. Single crystal conductivities are sometimes difficult to reproduce due to flaws or impurities in individual crystals and poor electrode-crystal contacts. For TTF-TCNQ, as an example, single crystal conductivities have been reported over a range of $\sigma = 10^2 - 10^3$ at room tempedrature.[1] Pressed powder conductivities are fairly reproducible, but are usually 10^2 times

lower than found for the single crystal.[7] Overcoming these difficulties will be essential to make organic metals a useful class of compounds. In the future, complexes using the tellurium analogues of some of the successful donors known at the present, such as HMTSF and TMTSF, may show higher conductivity in organic metals than have been observed so far. Development of suitable organic acceptors other than TCNQ, such as the tetrahalobenzoquinones, will create new possibilities for organic complexes with high conductivity

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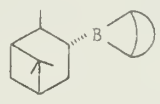
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ASYMMETRIC SYNTHESIS OF ALCOHOLS VIA ORGANOBORANES

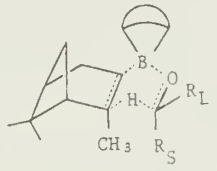
Reported by Burnell Lee October 29, 1984

Many synthetically-targeted, naturally-occurring compounds are chiral, and effective synthetic strategy must develop the appropriate enantiomer. One method of accomplishing this is to use "asymmetric synthetic reactions."[1] This report deals with the chiral non-racemic synthesis of alcohols from aldehydes and ketones with chiral organoboranes and organoborohydrides.[2] The development of chiral organoborane reagents has been successful for the asymmetric reduction of alkyl ketones in 57 to 90% ee.[3]

Midland found that hydroboration of (+)-2-pinene with 9-borobicyclo[3.3.1]nonane (9-BBN) produces a very effective reducing agent, alpine-borane(1).[4,5] Reduction of ketones with 1 proceeds through β-hydride transfer from the pinane borate to the keto carbonyl via a proposed 6-membered exo "boat-like" transition state **2**.[3b] The reduction occurs slowly at room temperature and atmospheric pressure in neat solutions (7-14 days).[3a] Heating the solution accelerates the



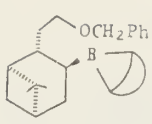
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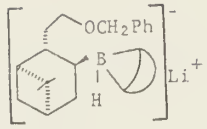
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reaction but decreases the asymmetric induction, while high pressure (6000 atm) accelerates the reaction (1-3 days) and also increases the asymmetric induction.[3b] The n-alkyl ketone, 2-octanone, was reduced in one day (63% yield, 58% ee) as was the α-branched ketone, 3-methyl-2-butanone (47% yield, 83% ee). The absolute configuration of the product is predictable from the proposed 6-membered transition state by placing the ketone substituents according to steric bulk as indicated in **2**,[3b] with the smaller substituent (R_S) interacting 1,3-diaxially with the 3-methyl group of the reducing agent. Alcohols of opposite configuration can be obtained through the use of (-)-α-pinene to form the enantiomer of **1** or the use of nopol (as its benzyl ether) to form reducing agent **3** (NB-enantrane).[6,7] The chiral α-pinene and nopol ether[6] can be recovered from the reduction reactions of **1** and **3** without loss of optical activity.

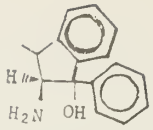
Treatment of **3** with t-BuLi at -78 °C generates a new chiral reducing agent **4** (NB-enantride)[8] that reduces alkyl ketones rapidly at -100 °C (70% yield, 30-79% ee), with absolute configurations opposite



3



4

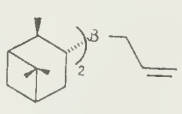


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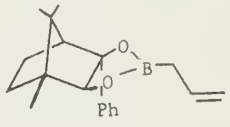
those obtained with **3**. Another reducing agent of uncertain structure is made from the chiral amino alcohol **5** and 2 equivalents of borane.[3c] Alcohol **5** is prepared from (s)-valine in two steps in 56% yield. This reagent is capable of reducing both 2-hexanone and 3,3-dimethyl-2-butanone in quantitative yield at 30 °C in 1h in 55% and 73% ee, respectively. Alcohol **5** can be recovered from the reaction mixture in 80% yield after recrystallization.

Reagents **1** and **3** have also been successful in the asymmetric reduction of prochiral ketones, which bear an electron-withdrawing group on the α-carbon at 25 °C, in a matter of hours, e.g., α,β-acetylenic ketones to chiral 2° propargyl alcohols (85-98% ee).[3b,8,9] From these, several sex pheromones containing a 4-substituted γ-lactone function have been synthesized,[10] as well as chiral α- and β-hydroxy acids.[11] Alpine-borane has also been used to reduce α-ketoesters[12] and α-haloketones[13] asymmetrically to α-hydroxy esters and halohydrins (75-95% ee). The β-dialkylamino alcohol ubine was synthesized from the asymmetric reduction product originating with bromoacetophenone.[13]

The use of β-allyldiisopinocampheylborane (**6**) as the allylation reagent for both alkyl and aryl aldehydes has induced excellent asymmetry (83-96% ee) in the formation of allyl 2°-alcohols.[14] Chiral allylborane **7** effectively produced homoallylic alcohols in non-racemic form (~70% ee) with a variety of aliphatic aldehydes but was less successful with α-unsaturated aldehydes.[15]



6



7

In summary, the reagent prepared from **5** and borane is the easiest to use in reducing alkylketones but the least studied thus far. Reagents **1** and **3** are also good for alkyl ketones but have been most successful with ketones bearing an electron-withdrawing group on the α-carbon. Allyl borane **6** is a more versatile allylation reagent for both alkyl and aryl aldehydes than **7**.

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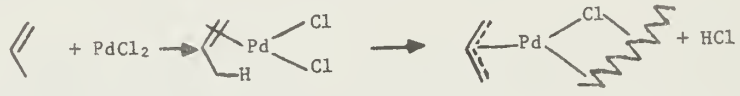
MECHANISTIC STUDIES ON THE FORMATION OF π-ALLYL PALLADIUM COMPLEXES

Reported by Douglas R. Chrisope November 1, 1984

During the past decade π-allyl palladium complexes have become useful as synthetic intermediates in stoichiometric and catalytic reactions.[1,2] Efforts to elucidate the mechanism of their formation from olefins, however, have met with little success. The reaction may be viewed formally as a metal insertion into a carbon hydrogen bond, but there is little evidence as to whether this formality is correct.

It is accepted that $PdCl_2$ or other Pd(II) species form a π-complex with olefins[3] prior to the critical step in which an allylic hydrogen is removed as shown in Scheme I.

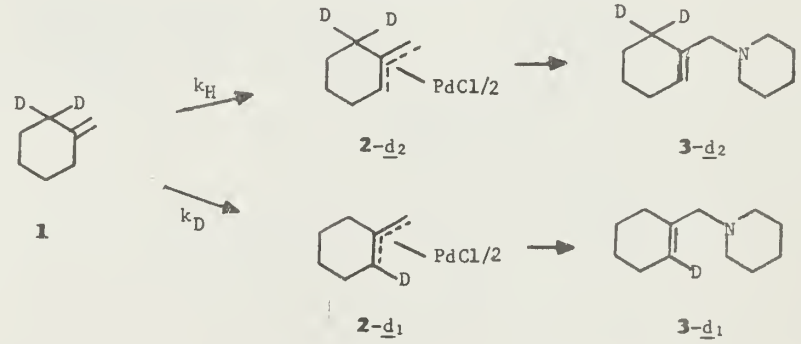
Scheme I



Mechanistic proposals for this hydrogen removal include: 1) abstraction as hydride by palladium;[4] 2) proton abstraction by external bases;[4c,5] 3) proton abstraction by a ligand, usually chloride.[6] The experimental evidence for each of these mechanisms is limited and inconclusive. In this report we will present evidence which rules out one choice, namely hydride abstraction by palladium.

The allylically deuterated olefin **1** was allowed to react under various conditions to form the π-allyl palladium complexes **2**-$\underline{d_2}$ and **2**-$\underline{d_1}$ as shown in Scheme II. Following conversion of the mixture of complexes

Scheme II



to the corresponding amine derivatives **3**, the ratio of **3**-$\underline{d_2}$ to **3**-$\underline{d_1}$ was determined by MS and ^1H NMR analysis, which gives directly the product

isotope effect. The reaction conditions and their corresponding values of k_H/k_D are collected in Table I.

The large isotope effect for reactions in DMF, $k_H/k_D = 5.9$, is roughly the maximum expected for cleavage of a typical carbon-hydrogen

Table I

Product isotope effects for conversion of **1** to **2**, determined from ratio of **3**-$\underline{d}_2$ to **3**-$\underline{d}_1$

Entry	Reaction Conditions	k_H/k_D
1	DMF/$PdCl_2$	5.9 ± 0.2
2	C_6H_6/$PdCl_2$, 2 equiv DMF	5.3 ± 0.2
3	AcOH/$PdCl_2$, NaCl, NaOAc, $CuCl_2$	3.6 ± 0.2
4	70% aq AcOH/$PdCl_2$, NaCl, $CuCl_2$	3.8 ± 0.2

bond at 60 °C in the absence of quantum mechanical tunneling.[8] This magnitude implies a nearly linear and symmetrical transition state for the transfer of H to another atom.[9] Consideration of likely transition state structures for hydride transfer to palladium leads to the expectation of low isotope effects for two reasons: 1) electrophiles generally approach the bonding electrons of a carbon-hydrogen bond, creating a non-linear transition state.[10] Typically, $k_H/k_D = 1.5 - 2.5$ in intermolecular hydride transfers, but some larger values are known.[11] 2) The intramolecular transfer of hydride in the present reaction would approximate a four-membered cyclic transition state with an isotope effect estimated by model calculations to be ca. 2.[11] In order to obtain an experimental isotope effect for such a reaction, we determined the kinetic isotope effect in the isomerization of methylenecyclohexane to 1-methylcyclohexene by Pd(II). This reaction is believed to proceed via an intramolecular hydride transfer, and the observed kinetic isotope effect of 1.8 ± 0.5 supports such a mechanism. The large isotope effects observed in π-allyl complex formation appear to rule out a similar hydride transfer in both DMF and AcOH solvents.

It is difficult to distinguish between the two remaining suggested mechanisms at this point. Examination of molecular models shows one chloride ligand to be suitably situated to accept an ejected proton with a slightly bent transition state. The elimination of HCl in concert with the electronic reorganization at the metal is appealing in that no added base is required. Efforts are underway to determine what is removing the proton and whether the responsible species is complexed to palladium at the time.

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REACTIONS OF DIAZONIUM SALTS IN MICELLES

Reported by Joseph A. Van Gompel November 5, 1984

Diazonium salts, which have been known for many years as a source of phenyl cation in addition to being precursors to azo compounds,[1] can be prepared by the reaction of the corresponding amine with sodium nitrite in acidic aqueous solution, or in organic solution using nitrous acid esters.[2] They are relatively unstable both thermally and photochemically, with typical rate constants of reaction on the order of 10^{-4} to 10^{-6} s^{-1} at 25° C, depending on substituents.[3] Products from thermal vs. photolytic reactions are similar in structure, but relative yields of products change depending on substituents present and method (photolytic or thermal) of activation.

The products of reactions of diazonium salts can be influenced by environment, and such influence is especially obvious in micellar systems. The structure of micelles is not as straightforward as initially assumed by Hartley.[4] Several experiments using techniques such as ^{1}H NMR,[5] ^{13}C NMR,[6] external fluorescence quenching (quenching of a hydrophobic species by a hydrophilic species in a micellar system),[7] pulse radiolysis,[7] ORD,[8] and others,[6,7,9] in which the data obtained are sensitive to solvent polarity, suggest that the interior of a micelle in aqueous solution is actually relatively polar. This polarity is due in large part to coulombic repulsion of the similarly-charged polar head groups and resultant admission of both counterions and water as far as perhaps one-third of the distance to the core of the micelle.

The photodecomposition of diazonium salts can be effected either by direct photolysis or by irradiation of another chromophore which can then undergo energy transfer to cause extrusion of N_2 and generation of an aryl cation, or electron transfer can take place with the formation of a phenyl radical. Direct irradiation of benzenediazonium tetrafluoroborate (BDTF) in either homogeneous aqueous phase or in micellar solution yields phenol almost exclusively (95%).[10] By contrast, triplet sensitization by phenanthrene in a dodecyltrimethyl-ammonium bromide system gave a product mixture of benzene (42%), bromobenzene (27%), and phenol (31%), suggesting that the BDTF must be relatively deep in the micelle where the local bromide concentration is high, so sensitization by phenanthrene can occur. In direct photolysis, most of the BDTF is repelled by the positively-charged Stern region where the bromide counterions are located, hence yielding hydrolysis product. The 42% yield of benzene is explained by electron transfer to form the phenyl radical which then abstracts H· from some other species.

Both electron-transfer quenching[11] and energy-transfer quenching by diazonium salts in micellar systems[12] have been reported independently.

Work by Moss[13] showed that micellar dediazoniation has dramatic effects on the course of reaction. Compounds were developed which incorporated the diazonium cation in the micelle itself. Comparison with a control diazonium salt which was incapable of micellization showed that counterion incorporation (Br-) occurred in >95% yield in micelles, whereas phenol generation was the predominant (>95%) product in the non-micellar system. Bromide incorporation did increase in the latter system with added NaBr. A series of reactions in which alkyldiazonium salts in various concentrations were decomposed in the presence of either bromide or chloride ions showed a very sharp increase in the ratio of halide vs. alcohol products at and above the critical micelle concentration (CMC).[14] These results, too, can be explained by the high local concentration of counterions (Br-, Cl-) in the Stern region of the micelle.[15] The control of reactions of diazonium salts by the nature of the micellar environment needs further understanding but offers the promise of future application.

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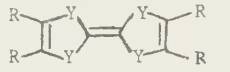
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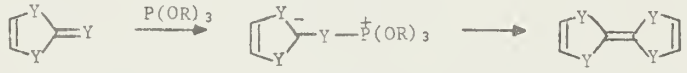
SYNTHESIS OF 1,1',3,3'-TETRATHIA-, TETRASELENA-, AND TETRATELLURAFULVALENES

Reported by Cynthia K. Loop November 8, 1984

Various synthetic methods for 1,1',3,3'-tetrathia-, 1,1',3,3'-tetraselena-, and 1,1',3,3'-tetratellurafulvalenes (**1**) have been developed over the years due to the interest in utilization of these compounds as π donors in charge transfer complexes for studies of unusual conductivity. Since a good review of the syntheses of these compounds appeared in 1976,[1] this paper will emphasize the work done since the published review.

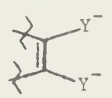
1  R = H, CH_3, CF_3, CN, CO_2H, CO_2Me, etc.; Y = S, Se, Te

One approach to the preparation of these compounds involved the coupling of the corresponding thiones or selones by treatment with triphenylphosphine,[2] trialkyl phosphites,[3] or dicobalt octacarbonyl.[4] The yields varied depending on the thiones or selones used and were in the ranges of 30-65%, 30-90%, 20-45% for the three reagents, respectively. Other routes include the coupling of 1,3-dithiolium salts



which produced the corresponding tetrathiafulvalenes in 30-99% yields[5] and the use of a nickel complex which produced a tetrathiafulvalene in 50-60% yield.[6]

Other methods not involving a coupling step have been reported. For example, the combination of substituted acetylenes and carbon disulfide or carbon diselenide under conditions of high pressure and elevated temperature gave the desired fulvalenes in 85-90% yields.[7] A second approach was the conversion of 1,3,5,7-tetrathiapentalene-2,6-dione by the treatment with propargyl halide derivatives to tetrathiafulvalenes in about 35% yield.[8] A third route employed the treatment of **2** with tetrachloroethylene. This scheme has been used to prepare tetrathiafulvalenes and tetratellurafulvalenes in yields of 10-30%.[9]

2  Y = S, Te

Research on compounds of type **1** is proceeding actively, and these compounds are being used to test their ability to form superconducting

charge transfer complexes.[10] Researches on the preparation of polymers containing tetrathiafulvalene units have also been reported.[11] Nevertheless, there is need for convenient, high-yield synthetic methodology for these fulvalenes in general.

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RATES OF ELECTRON-TRANSFER REACTIONS; EXPERIMENTAL VERIFICATIONS OF THE MARCUS INVERTED REGION

Reported by Tom Autrey November 12, 1984

The simplest chemical reaction is the transfer of a single electron from one molecule to another, no bonds need to be broken, no bonds need to be formed. For an electron transfer reaction, the rate constant can be evaluated by equation (1) where Z is the collisional number in

$$k_{et} = Ze^{-(\Delta G^{\ddagger}/RT)} \qquad (1)$$

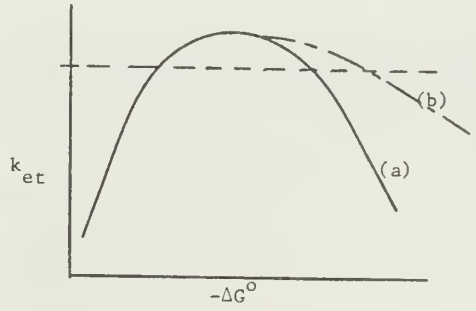
solution, taken as 10^{11} M^{-1} s^{-1} and $\Delta G^{\ddagger}$ is the free energy of activation. Almost 30 years ago Marcus[1] developed a theory that has since been elaborated,[2] which predicted a correlation between the thermodynamics and the kinetics of outer-sphere electron transfer reactions. The theory predicts that the free energy of activation depends quadratically on the free energy change of the electron transfer reaction, $\Delta G°$, equation (2). W_r is the free energy change required

$$\Delta G^{\ddagger} = W_r + (1/4\lambda)\ (\Delta G^{o} + \lambda)^2 \qquad (2)$$

to bring the reactants into the positions they occupy in the activated complex and λ is the free energy change required to reorganize the solvent molecules into the positions they occupy in the activated complex. The Marcus theory thus predicts that the rates of electron transfer should be relatively slow for weakly exothermic reactions, increase to a maximum for moderately exothermic reactions, and then decrease again to slower rates for highly exothermic reactions. This

Figure 1

Plot of electron-transfer rate constant as a function of reaction exothermicity as predicted by Marcus theory. Curve (a) is predicted by classical theory. Curve (b) is predicted by quantum mechanical theory, in which electron tunneling is responsible for faster rates at high energies.



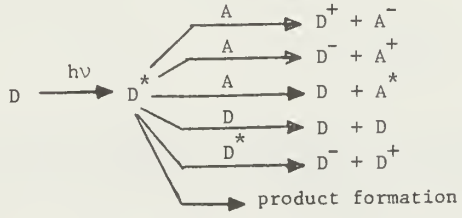
inverted behavior is a consequence of simultaneously requiring a conservation both of energy and nuclear position for electron transfer.

In order for the reaction to occur, the reactants must first reorient themselves to a nuclear configuration similar to that of the products. The second condition requires the products to have vibronic excitation equal to the exothermicity of the reaction. The maximum rate should occur when the standard free energy change of the reaction, $\Delta G°$, equals the energy required to reorient the solvent molecules into the positions they occupy in the activated complex.

The Marcus theory contradicted classical theories of electron transfer reactions, and seemed to contradict almost all experiments designed to confirm it.[3] Herein will be reported recent experimental evidence that has confirmed the existence of the Marcus inverted region. The important experimental parameters will be discussed, and some reasons why earlier experiments did not reveal the rate restrictions will be presented. Finally, the usefulness of this behavior will be explained in terms of solar energy efficiency.

Oxidative quenching

Because reactions of excited states can be highly exothermic, their use in the search for the Marcus inverted region could lead to some promising results. Photo-induced electron transfer reactions can be followed by observing the quenching of luminescent excited states by an electron acceptor, oxidative quenching, or by an electron donor, reductive quenching. When the rate of electron transfer reactions by oxidative or reductive quenching is measured, it is important to control all possible routes of luminescent decay equations (3)-(8). In



(3)
(4)
(5)
(6)
(7)
(8)

addition to the oxidative quenching (3) or the reductive quenching (4) of an excited state, other mechanisms for luminescent decay exist: energy transfer (5), quenching by the ground state (6), disproportionation (7), and formation of secondary photo-products (8). In order to detect a decrease in the rate of luminescent quenching by electron transfer at high exothermicities, it will be important to control the reaction

pathways, since quenching by more than one route will mask the real rate of electron transfer by making it appear faster.

Sutin et al.[4] studied the oxidative quenching of excited state Ru(II) complexes by various ground state metal complexes. The Ru(II) complexes are known to be powerful reducing agents, and their reactions with metal complexes are highly exothermic equation (9).

$$*RuL_3^{2+} + ML_3^{3+} \longrightarrow RuL_3^{3+} + ML_3^{2+} \qquad (9)$$

It had been shown that the quenching reaction of $*Ru(bpy)_3^{2+}$ by $Cr(bpy)_3^{3+}$ did not take place by an energy transfer mechanism,[5] and the products detected by flash photolysis were shown to be those expected from the oxidative quenching mechanism.[6] By analogy, the other metal quenchers were to behave accordingly.

Table I

Ground state complexes used to quench luminescent Ru(II) complexes and the driving force for the reaction, ΔE^o.

Donor	Acceptor	ΔE^o (V)
I	$Cr(bpy)_3^{3+}$	0.58
II	$Cr(bpy)_3^{3+}$	0.69
I	$Os(bpy)_3^{3+}$	1.65
II	$Os(bpy)_3^{3+}$	1.76
I	$Ru(4,4'-(Ch_3)_2\ bpy)_3^{3+}$	1.93
II	$Ru(4,4'-(CH_3)_2\ bpy)_3^{3+}$	2.04
I	$Ru(bpy)_3^{3+}$	2.09

Donor I = $*Ru(bpy)_3^{2+}$

Donor II = $*Ru(4,4,'-(CH_3)_2\ bpy)_3^{2+}$

bpy = bipyridine

The lifetimes of the excited states were measured using flash photolysis techniques. Pseudo first-order rate constants were obtained by irradiating solutions containing the Ru(II) metal complexes in the presence of excess quencher at the absorbance maximum of the complex and by monitoring the emission of the excited state complex.

Using the Stern-Volmer analysis, the rate of electron transfer could be calculated from the measured lifetimes equation (10), where

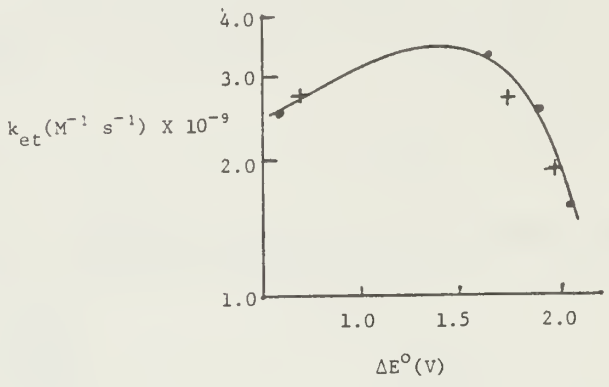
$$I_o/I = 1 + k_{et}\tau_{es}[Q] \qquad (10)$$

I and I_o are the intensities of luminscence measured with and without quencher present, respectively, τ_{es} is the lifetime of the excited state, and [Q] is the quencher concentration.

A plot of k_{et} versus ΔE^o yielded a curve displaying the Marcus "inverted" region.

Figure 2

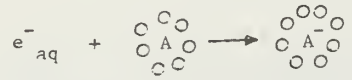
Quenching rate constant as a function of driving force for electron-transfer. (·) for *Ru(bipy)$_3^{2+}$, (+) for *Ru(4,4^1(CH$_3$)$_2$ bipy)$_3^{2+}$.



Sutin concluded by arguing that any other mechanisms for quenching the Ru(II) complexes would only strengthen their case because the rate could only be reduced by eliminating other routes of decay.

Micellar systems

The use of the hydrophobic and electrostatic interactions of micellar systems offers some advantages that cannot be found in homogeneous environments. Organic acceptors solubilized in micellar solutions are known to react with hydrated electrons by a tunneling of the electron through the micellar electric double layer[7] equation (11). It has been shown that hydrated electrons do not migrate



(11)

into acceptor-free micelles, nor do they chemically react with them.[8] The rate of electron transfer will be affected by (a) the distance the electron has to tunnel, (b) the charge of the micelle, and (c) the potential difference between the aqueous phase and the organic phase of the surfactant interface.

Henglein[9] measured the effects of electron transfer rates in both cationic cetyltrimethylammonium bromide (CTAB), and anionic sodium laural sulfate (SLS) micelles between various organic acceptors solubilized within the micelle and aqueous electrons generated by pulse radiolysis. Pulse radiolysis generates free electrons by bombarding a solution with a source of high energy electrons from a linear accelator equation (12). The experiment was designed using a concentration of micelles at least 100 times greater than the concentration of acceptor

$$2H_2O + e^- \longrightarrow H_3O^+ + HO^\cdot + e^-_{aq} \qquad (12)$$

to ensure that no more than one acceptor would reside in any one micelle. The rate of reaction of the aqueous electron with each acceptor was followed by recording pseudo first-order decay of the electron's absorption, λ_{max} = 600 nm, or by observing the increase in the absorption of the reduced organic acceptor. A large range of exothermicities was achieved by using acceptors of various reduction potentials (Table II). It was found that the rate of transfer between solvated electrons and the acceptors in cationic micelles did not depend

Table II

Organic acceptor molecules solubilized within the micelles and their respective reduction potentials.

Acceptor	-ΔG(eV)
nitrohexane	0.2
nitroanthracene	0.4
tetranitromethane	0.8
1,2,4,5-tetracyanobenzene	1.1
p-chloranil	1.6

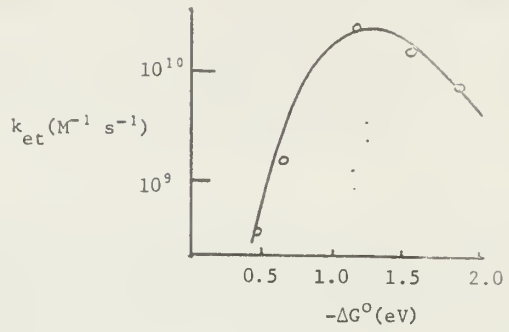
on the reaction exothermicity because of the long residence time of the electron in the positive field of the micelle. To decrease the effect of the repulsive potential developed in anionic micelles, a salt, sodium sulfate, was added to the reaction mixture. The rate constants were calculated using the half-lives measured from the absorption decays of the aqueous electron in the presence of excess organic acceptor equation (13). The rate restrictions predicted by the Marcus theory

$$k_{et} = \frac{\ln 2}{\tau_{1/2}[A]} \qquad (13)$$

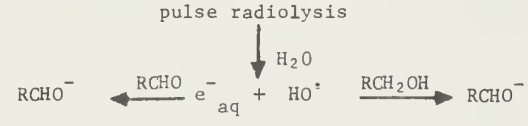
were observed in the reactions of aqueous electrons with organic acceptors in the anionic micelles.

Figure 3

Electron-transfer rate constants as a function of free energy of the electron-transfer reaction.



Another approach would be to vary the donor and keep the organic acceptor the same. Hydroxide radicals are known to react with α-alcohols, and aqueous electrons are known to react with aliphatic aldehydes or ketones to yield ketyl radicals equation (14).



(14)

The redox potentials of the ketyl radicals were determined by polarographic observations of the corresponding aldehydes or ketones.

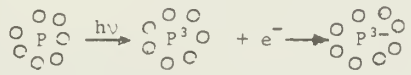
Table III

Ketyl radicals generated by pulse radiolysis of the corresponding aldehyde or ketone and their reduction potentials.

donor	acceptor	
	singlet pyrene	triplet pyrene
	-ΔG(eV)	-ΔG(eV)
CO_2-	0	-2.1
CH_2O^-	+0.3	-1.0
CH_3CHO^-	-0.1	-2.0
$CH_3COCH_3^-$	-0.4	-2.5

Using this approach Henglein[10] measured the rate of electron transfer from the ketyl radicals to pyrene in its singlet and triplet states. This was accomplished again by using an excess of surfactant molecules to ensure that only one acceptor resided in any one micelle at

a time. The aqueous solution containing the corresponding aldehyde and alcohol was exposed to a pulse of high energy electrons to generate the ketyl radicals. In this experiment, the rate of electron transfer from the radical to the organic acceptor across the micelle double layer was measured by monitoring the increase in the pyrene anion absorption. In the case where the pyrene triplet was to be the acceptor, the reaction solution was exposed to a pulse of light to generate the triplet pyrene



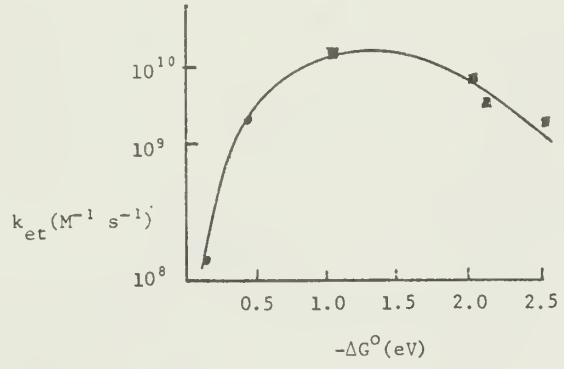
(15)

before pulse radiolysis equation (15). The rate of electron transfer increased with increasing exothermicity for the singlet pyrene while the rate decreased with increasing exothermicity for the triplet pyrene.

A graph of the results demonstrated the Marcus inverted behavior.

Figure 4

Electron-transfer rate constants as a function of free energy changes for the transfer of an electron from the radical anion to pyrene in its singlet state (•) and to pyrene in its triplet state (■).



Intramolecular systems

Another design that would offer a method to separate the acceptor and donor groups would be the placement of a rigid spacer in between them (A - spacer - B). A large range of exothermics could be achieved by varying either one group or the other. Pulse radiolysis could be used to generate electrons that could be trapped by the model compound. Using photometric techniques the rate of intramolecular electron transfer, from A to B or B to A, could be measured.

Miller and Closs[11] have taken advantage of this design. They synthesized a series of compounds containing two molecular groups with different electron affinities separated by a rigid spacer. They kept

Figure 5

Spacer molecule, 5α-androstane, distance edge to edge 10Å. The A groups were varied and the B group was biphenyl.



B the same, B = biphenyl, and varied the A group to achieve the range of exothermicities they needed.

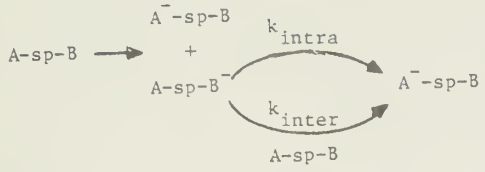
Table IV

A groups built onto spacer molecule, B is biphenyl, and the driving force for the reaction, transfer of an electron from biphenyl to the acceptor, ΔG^{o}.

A group	$-\Delta G^{o}$(eV)
2-naphthyl	0.05
9-phenanthryl	0.16
1-pyrenyl	0.52
hexahydronaphthoquinon-2-yl	1.23
2-naphthoquinonyl	1.93
2-benzoquinonyl	2.10
5-chlorobenzoquinone	2.29
5,6-dichlorobenzoquinon-2-yl	2.40

B-group = 4-biphenylyl

The A- sp -B molecules were dissolved in a solution of methyltetrahydrofuran, MTHF, and irradiated with a pulse of high energy electrons using a linear accelerator. The concentration of the model compound, A-sp -B, was high enough to ensure that there would only be one electron in any model compound. The electrons generated by the irradiation were captured by the A and B groups with statistical probability. As a result of the differences in electron affinities between the various acceptors and donors, A being greater than B, a state of nonequilibrium is created. The rate of equilibration, transfer of an electron from B to A, measured photometrically, consisted of two rates, the intramolecular rate they were looking for and an intermolecular rate that had to be corrected for equation (16).



(16)

The rates of intermolecular electron transfer were measured by subjecting a solution of monofunctional compounds A-spacer and B-spacer to the same conditions. Again the electrons were captured by the A and B groups with statistical probability and the rate of equilibration was measured equation (17). Assuming the rates of monofunctional

$$A\text{-sp} + B^{-}\text{-sp} \xrightarrow{k_{inter}} B\text{-sp} + A^{-}\text{-sp} \qquad (17)$$

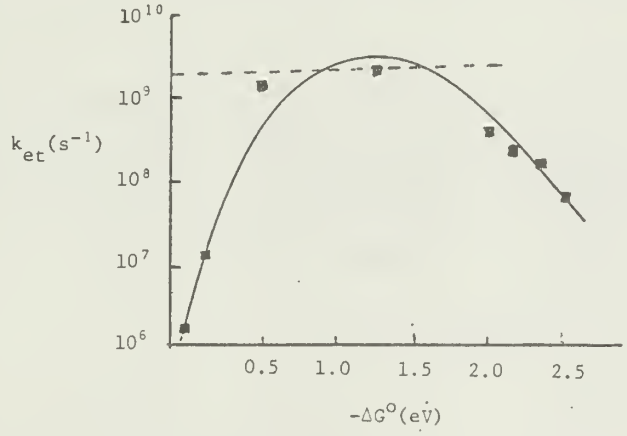
intermolecular electron transfer are comparable to the rates of difunctional intermolecular electron transfer, the rates of intramolecular electron transfer were calculated according to equation (18). The rates of intramolecular electron transfer plotted as a

$$k_{intra} = k_{obs} - k_{inter} \qquad (18)$$

function of reaction exothermicity demonstrated the Marcus "inverted" behavior.

Figure 6

Intramolecular electron-transfer rate constants as a function of free energy change for electron-transfer in methyltetrahydrofuran, MTHF. Dashed line is limit of detection.

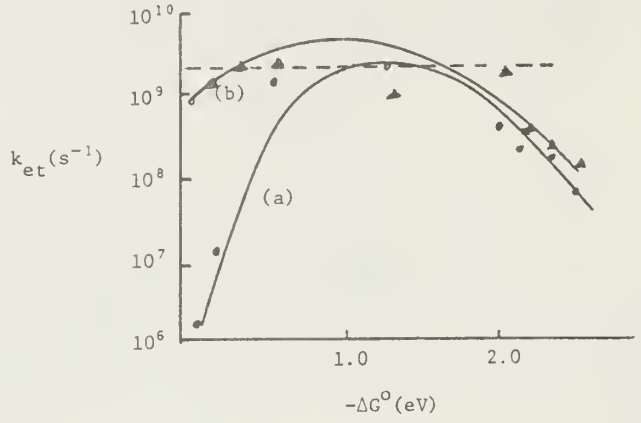


According to the Marcus Theory, the maximum rate of electron transfer will occur when the free energy change of the reaction matches the free energy required for the solvent to reorganize. The energy

at which the maximum will be reached should depend on solvent polarity. It would require less energy to reorganize a nonpolar solvent than it would take to reorganize a polar solvent. To test this hypothesis, Miller and Closs repeated their experiments in a nonpolar solvent, isooctane, and compared their results with the experiments in MTHF. They found that the maximum of the curve was displaced to a lower energy as expected.

Figure 7

Comparison of data for experiments in (a) MTHF and in (b) isooctane; the maximum rate is at lower energies for isooctane. Dashed line is limit of detection.



The search for the Marcus inverted region has often led to contrary results. Some reasons why certain experiments have not produced inverted behavior have already been mentioned. Experiments attempting to measure the rate of electron transfer by quenching mechanisms is important to control the pathways of decay. Other reasons given for not observing the inverted behavior included the formation of products in the excited states and competitive pathways at high reaction exothermicity.

One natural application of this inverted behavior could be its use in solar energy conversion. We can imagine a design where a donor atom is raised to an excited state by the absorption of a photon of sunlight. It can be quenched by an acceptor in a weakly exothermic reaction to create an ion pair equation (19). The reaction to form ground state

$$D^{*} + A \xrightarrow[\text{small}]{-\Delta G^{o}\ \text{is}} D^{+} + A^{-} \xrightarrow[\text{large}]{-\Delta G^{o}\ \text{is}} D + A \qquad (19)$$

$D^{+} + A^{-}$ $\downarrow$ energy harvest

products could be very exothermic, so exothermic that it lies in the Marcus inverted region resulting in a relatively slow rate of formation of the ground state products. Meanwhile the energy from the highly exothermic intermediates could be harvested to do some useful work.

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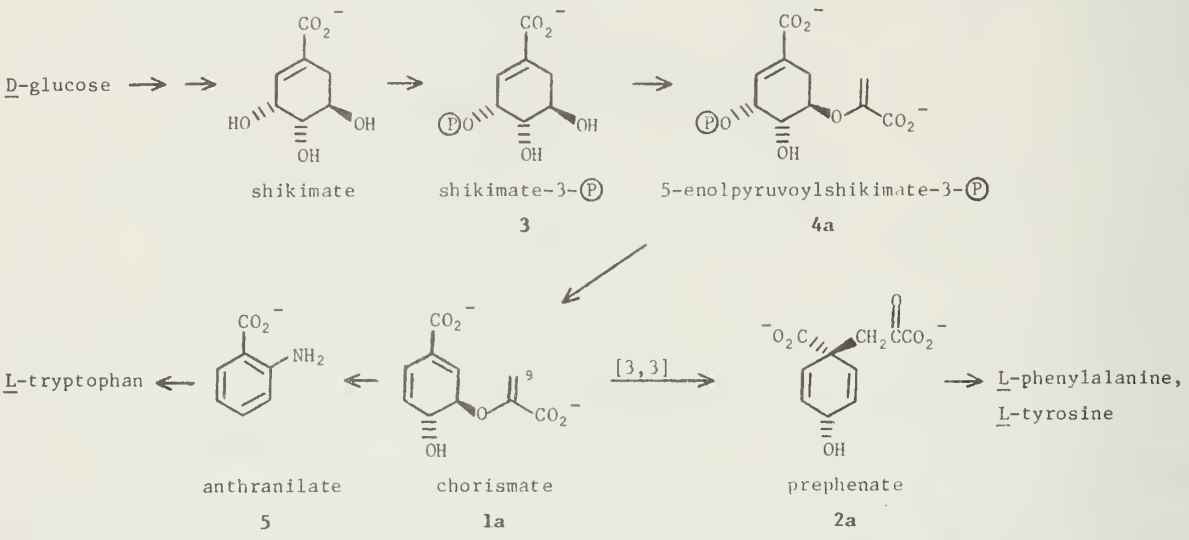
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THE BIOSYNTHESIS AND REARRANGEMENT OF STEREOSELECTIVELY LABELED CHORISMATE

Reported by Martha Schlicher November 15, 1984

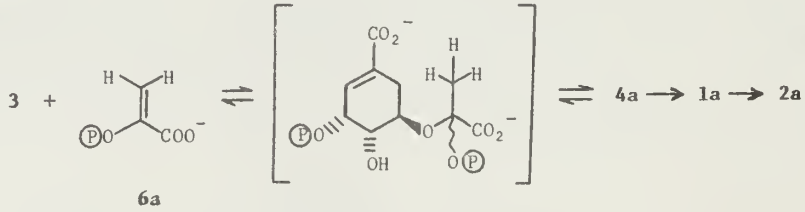
Chorismic acid is of primary importance as a major branch point in the shikimic acid pathway (Scheme I).[1] Its novel conversion to prephenate (**2a**), catalyzed by chorismate mutase, involves the only known example of a pericyclic reaction in primary metabolism.[2] Chorismate biosynthesis from phosphoenolpyruvate, PEP (**6a**), is catalyzed by the

Scheme I



enzyme 5-enolpyruvoylshikimate-3-phosphate synthetase on a mechanistic pathway of addition/*trans*-1,4-elimination of phosphate (Scheme II).[3-5] When followed by the [3,3]-sigmatropic shift to prephenate, it provides a route to the aromatic amino acids phenylalanine and tyrosine in bacteria, fungi, and plants.[6] The conversion of **1a** to **2a** occurs rapidly

Scheme II



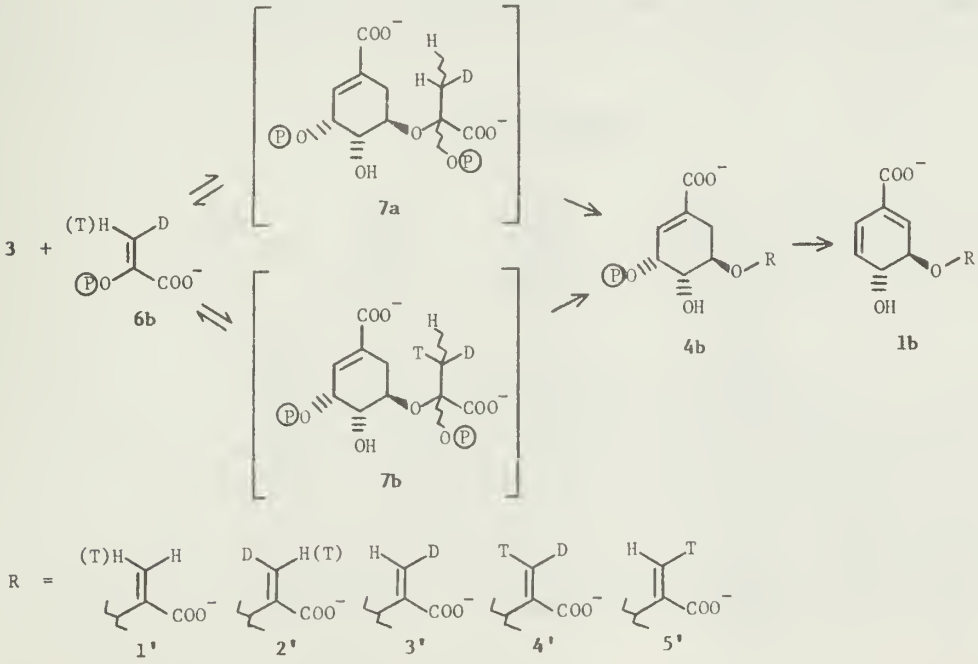
in vitro ($t_{1/2}$ = 30 min, 70 °C, pH 8). Enzymatically, following Michaelis-Menten kinetics, the rate increases by 2 x 10^6 at 37 °C.[7-9] Attempts have been made to determine the stereochemistry of chorismate

conversion to prephenate by inhibition studies and molecular orbital calculations.[9-11] Until the recent studies using stereoselectively labeled chorismate, however, the actual pathway had never been fully established.[12-14] This work has revealed new information on the geometry of the transition state of the chorismate mutase-catalyzed reaction and on the stereochemistry of the biosynthesis of chorismate from PEP.[12-15]

Two similar methods have been developed recently in an effort to prepare stereoselectively labeled chorismate biosynthetically.[12-14] In both cases, the biosynthesis proceeded by incubation of stereospecifically labeled **6a** with shikimate-3-phosphate (**3**) to generate 5-enolpyruvoylshikimate-3-phosphate (**4a**), an intermediate converted to **1a** by chorismate synthetase (Scheme II).[12,13] The major differences in the two methods are the source of preparation of the stereospecifically labeled PEP and the method of location of the label in the product. Alternatively, a recent chemical synthesis of stereoselectively labeled chorismate has been effected.[14]

By the first method, [9-^{2}H,^{3}H]-5-enolpyruvoylshikimate-3-phosphate (**4b**) was biosynthesized from stereospecifically labeled (E)- or (Z)-[3-^{2}H,^{3}H]PEP (**6b**), by the 5-enolpyruvoylshikimate-3-phosphate synthetase catalyzed reaction with **3** (Scheme III).[12] The stereospecifically labeled (Z)- or (E)-PEP used in the incubation was synthesized from [1-^{3}H]glucose or [1-^{3}H]mannose, respectively.[15b]

Scheme III



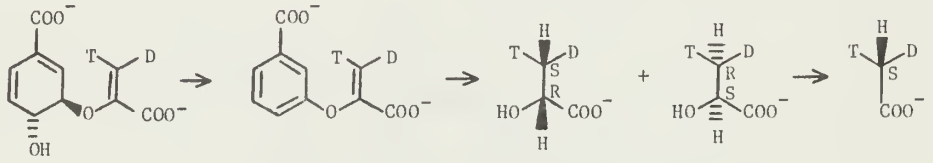
Conversion to (E)- or (Z)-[9-^{2}H,^{3}H]chorismate (**1b**) was effected by addition of chorismate synthetase to **4b**.

The incorporation of monodeuterated phosphoenolpyruvate led to a mixture of equally deuterio-labeled E and Z products (through **7a** and **7b**) due to free rotation of the intermediate methyl group.[4] A deuterium kinetic isotope effect varying from 2 to 3 with pH produced preferential retention of tritium in either the E or Z position, depending on the stereochemistry of the elimination.[5] The use of trace amounts of tritium as opposed to stoichiometric amounts of deuterium led to tritium incorporation in tracer levels.[5]

The stereochemistry of the addition-elimination reaction was determined by degradation of the resulting chorismate to acetate with subsequent analysis by the malate-fumarase assay (Scheme IV).[16-18] Chorismate was converted to (2R,3S)- and (2S,3R)-lactic acid (**8a**) by treatment with dimethyl sulfide, Wilkinson's catalyst, and lithium in ammonia. The resulting lactate mixture was separated by removal of S-lactate with lactate dehydrogenase. The remaining R-lactate was converted to chiral [^{2}H,^{3}H]acetic acid (**9a**) by Kuhn-Roth oxidation and was determined to be S by assay. The use of (Z)-[3-^{2}H,^{3}H]phosphoenolpyruvate led to (S)-acetate; accordingly, (E)-[3-^{2}H,^{3}H]phosphoenolpyruvate led to (R)-acetate as determined by F values.[19] Since (Z)-phosphoenolpyruvate leads to (Z)-chorismate, the synthetase addition reaction must occur with stereochemistry opposite to that of the elimination.

Identical results in the stereochemical determination of the addition-elimination reaction, based on the use of biosynthesized 9-[^{2}H,^{3}H]chorismate, were obtained in a slightly different manner using

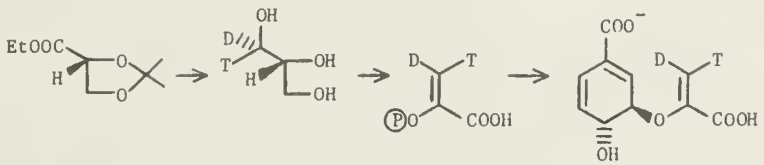
Scheme IV



1b **8a** **9a**

stereospecifically labeled PEP prepared from glycerol.[13] (E)-[3-^{2}H,^{3}H]Phosphoenolpyruvate (**6c**) was biosynthesized by incubation of (1R,2R)-[1-^{2}H,^{3}H]glycerol (**10**) with shikimate in cultures of Klebsiella pneumoniae mutant 62-1.[20] Continued incubation of **6c** produced stereoselectively labeled chorismate (**1c**) via the shikimate-3-phosphate intermediate (Scheme V). Klebsiella pneumoniae is

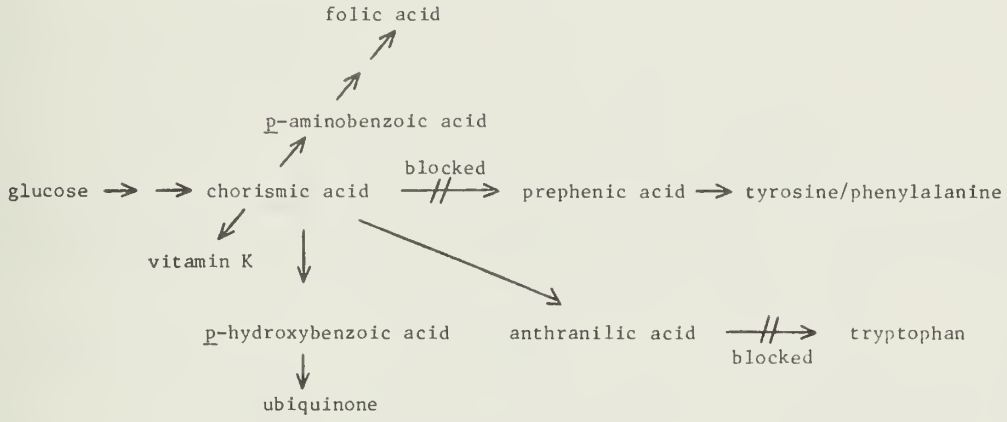
Scheme V



10 **6c** **1c**

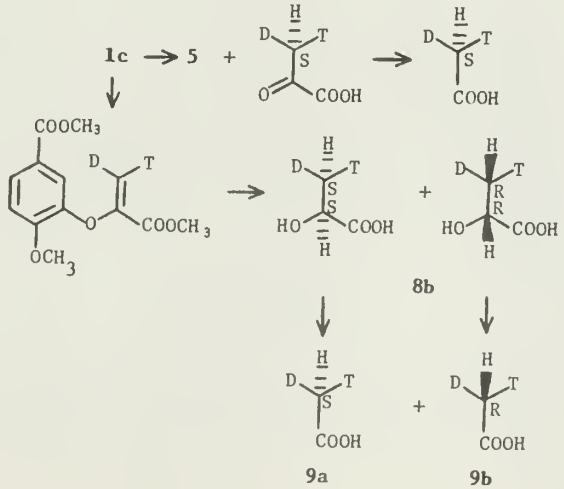
effective in that its pathways of significant chorismate conversion are halted by mutation, permitting chorismate accumulation (Scheme VI).[20]

Scheme VI



Determination of the chirality was achieved through the conversion of **1c** to acetate by incubation with anthranilate synthetase and lactate dehydrogenase followed by oxidation. The resulting acetate was assayed and found to have a 19% enantiomeric excess of (S)-acetate (Scheme VII).[19]

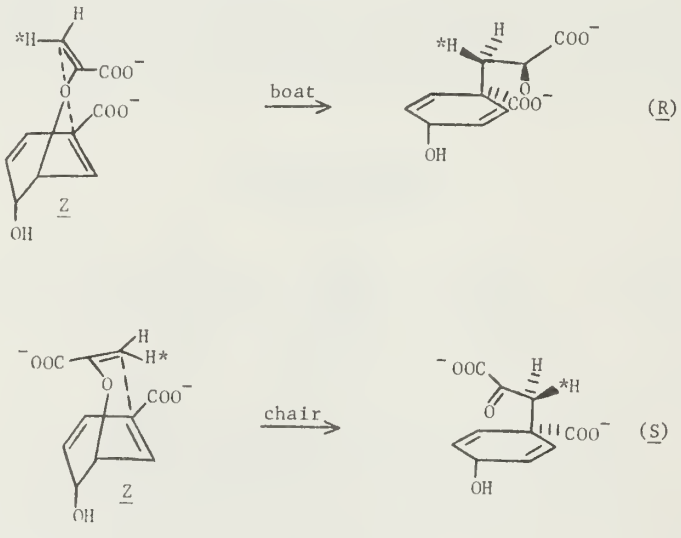
Scheme VII



Determination of the configuration about the chorismate double bond was also achieved by malate-fumarase assay.[16-18] Chorismate was degraded in a similar manner through aromatization, reduction with Wilkinson's catalyst, and finally with lithium in ammonia. Hydrolysis provided (R,R)- and (S,S)-lactate, (**8b**), due to the cis addition of hydrogen on both faces of the double bond. Conversion of L-lactate to pyruvate was effected by incubation with L-lactate dehydrogenase and NAD^+. D-Lactate was similarly converted with D-lactate dehydrogenase. Hydrogen peroxide oxidation of pyruvate (produced from L-lactate) generated (S)-acetate (**9a**).[21] Similarly, D-lactate produced (R)-acetate (**9b**). These results indicate an E configuration for chorismate synthesized from (E)-PEP, again suggesting addition-elimination steps of opposite stereochemistry.

Through the use of chorismate mutase inhibitors and molecular orbital calculations, the chair transition state has been proposed for the Claisen rearrangement of chorismate to prephenate.[9-11] It was realized at an early stage in the study of the reaction, however, that the stabilization of chair versus boat of less than 2 kcal/mol made clarification of the transition state unfeasible without the preparation of stereoselectively labeled chorismate and analysis of its prephenate product.[9,10] As outlined in Scheme VIII, the use of (Z)-[9-^{2}H,^{3}H]-chorismate as a substrate produces prephenate with an R center if the reaction proceeds through a boat transition state and with an S center if the reaction proceeds through a chair transition state.

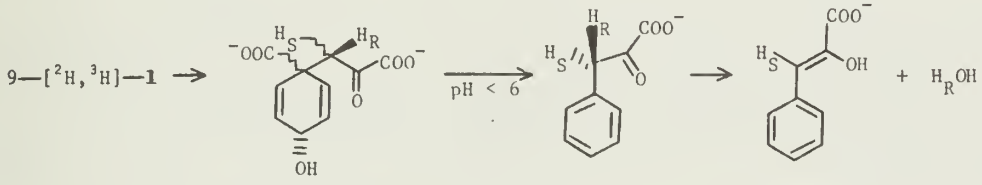
Scheme VIII



Transition state geometry was determined by conversion of the biosynthetically labeled chorismate, prepared from glucose, to prephenate by incubation with chorismate mutase.[15] These samples of chorismate had deuterium and hydrogen equally distributed at both C9 positions, while tritium was in tracer levels, 75% E or 75% Z.[11] The same was done for chemically synthesized chorismate samples which were 75% or more Z and 75% or more E by NMR.[14,15]

Degradation of prephenate to determine the location of the label was accomplished by spontaneous decarboxylative dehydration of prephenate below pH 6 (Scheme IX).[21] Labilization of the pro-R position of phenylpyruvate (**11**) occurs in the presence of phenylpyruvate tautomerase.[22] A simultaneous time-monitored run of these reactions indicated that when a random label of 9-[^{2}H,^{3}H]chorismate was used, a burst of tritium appeared in the solvent (50% of initial incorporation). When biosynthetically prepared Z compound was used, 20% of the tritium was lost, whereas when the same preparation of E compound was used, 67% was lost. Similar results were obtained with the chemical preparation. These results indicate a chair transition state where the Z proton of chorismate becomes the pro-S proton of prephenate.

Scheme IX



11

The synthesis, both chemically and enzymatically, of stereoselectively labeled chorismate has provided a means of unambiguous affirmation of both the mechanism of formation of chorismate from shikimate-3-phosphate and its mechanism of conversion to prephenate. This was accomplished in spite of the fact that complete stereospecificity of label introduction was not feasible, mainly due to the free rotation of the intermediate methyl group in the addition-elimination mechanism, by using the results of kinetic isotope effect studies.

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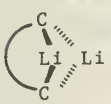
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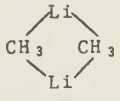
DILITHIOALKANES: STRUCTURE AND BONDING IN ORGANOLITHIUM COMPOUNDS

Reported by Craig C. Henderson November 19, 1984

Despite many theoretical[1] and experimental[2] studies on the ionic and covalent character of the carbon-lithium bond, its complex nature in simple organolithium compounds is still not well understood. Several important theoretical studies[3-5] on the structure and bonding in monomeric dilithiomethane, CH_2Li_2, have been reported, as well as experimental evidence[6] for the short-lived existence of monomeric CH_2Li_2 in the gas phase. The conclusion of Hoffmann[7] that electropositive substituents with both π acceptor and σ donor character, such as lithium, are effective in stabilizing a planar geometry about carbon relative to the normal tetrahedral geometry suggests that dilithiomethane is an excellent candidate for a simple planar carbon species. Other interest in dilithioalkanes has focused on the possibility of α,ω-dilithioalkanes undergoing an intramolecular dimerization to form **1**, analogous to the intermolecular dimerization observed for methyllithium, **2**.



1



2

Dilithiomethane

The first report of an organolithium compound with more than one lithium per carbon atom was the synthesis in 1955 of polymeric dilithiomethane, $(CH_2Li_2)_n$, by the Ziegler[8] pyrolysis of methyllithium (eq 1). Although the original systhesis was found to have poor reproducibility, a modified Ziegler synthesis[6] does give dilithiomethane in consistantly high yields (eq 2).

$$(CH_3Li)_4 \xrightarrow[1\ \text{atmos}]{230\text{-}240\ ^\circ C} (CH_2Li_2)_n + CH_4\ (g) \qquad (1)$$

$$(CH_3Li)_4 \xrightarrow[\text{vacuum, rapid stirring}]{223\text{-}226\ ^\circ C} \underset{95\text{-}96\%}{(CH_2Li_2)_n} + \underset{1\text{-}2\%}{(C_2Li_2)} \qquad (2)$$

Since organolithium compounds are highly associated both in solid phase and in solution, any experimental observation of monomeric dilithiomethane must be done in the gas phase. Dilithiomethane unfortunately does not have any observable vapor pressure below 650 °C and is stable above 200-250 °C only for a few seconds (eq 3), after

which the compound rearranges to give mostly C_2Li_2 (eq 4).[6] A short-lived, high temperature mass spectrum of dilithiomethane, therefore, was obtained by flash heating the dilithiomethane to 1500 °C in less than two seconds within 1 cm of the ionizing source of a mass spectrometer and then recording the spectrum within one second.[6] The resulting mass spectrum of the dilithiomethane vapor indicated that monomer through tetramer clusters are present in the gas phase.

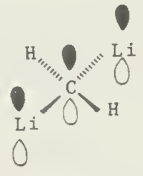
$$(CH_2Li_2) \xrightarrow[2\ sec]{1500\ ^oC} \underset{90\%}{(CH_2Li_2)} + \underset{2\%}{(C_3Li_4)} + \underset{8\%}{(C_3Li_2)} \qquad (3)$$

$$(CH_2Li_2) \xrightarrow[10\ min]{400\ ^oC} \underset{99\%}{(C_2Li_2)} \qquad (4)$$

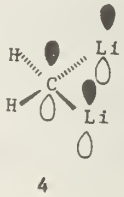
Although experimental data on dilithiomethane have been difficult to obtain, several ab initio calculations have been done to draw conclusions about the bonding and structure of the monomer. In an important theoretical study[3] of substituted methanes, Schleyer examined the ability of π acceptor and σ donor substituents, such as lithium, to lower the calculated energy difference (ΔE) between planar and tetrahedral geometry about carbon, assuming a singlet ground state configuration (Table I). The greater relative stabilization by cis

Table I[3]

molecule	ΔE (planar-tetrahedral) kcal/mole (4-31G basis set)
methane	168
cis-planar CH_2Li_2	10
trans-planar CH_2Li_2	47



3



4

lithiums (4) compared with trans lithiums (3) has been attributed to a more favorable overlap of the Li p orbitals with the central carbon p orbital in the cis arrangement to form a two-electron "homoaromatic" system with π Li-Li bond character, but no σ Li-Li bond character. This "homoaromatic" bonding description involving the Li p orbitals was supported by the Li-Li Mulliken overlap populations which were repulsive (-0.12 e) for the σ electrons, but bonding (+0.18 e) for the π electrons. This Mulliken electron population analysis led Schleyer to the conclusion that multicenter covalent bonding is important in the theoretical bonding description of cis-planar dilithiomethane.

Nevertheless, the use of Mulliken populations to determine bonding has been criticized[5] since Mulliken analysis assigns all electron density in any given orbital to the atom on which the orbital is centered regardless of the spatial extent of the orbital. Since lithium basis sets generally include very diffuse p orbitals, which have a maximum at a distance greater than the average Li-C bond length, electron density that is clearly near the carbon is assigned to the more distant lithium in this type of analysis. It has, therefore, been suggested that the Mulliken analysis erroneously assigns electron density to the p orbital of lithium, resulting in a more covalent description of the C-Li bond.[1d,5]

Another method for the analysis of the electron density in dilithiomethane has been promoted by Streitwieser and Baenrach.[5,9] In this method, electron densities are projected onto the plane determined by the carbon and two lithiums. Contour graphs of the projected electron density are then drawn to give a graphical representation of the distribution of electron density. Integration of these graphs over regions defined by the gradient vector gives the integrated spatial electron populations (ISEP) associated with each atom. For singlet planar and tetrahedral dilithiomethane, the ISEP for the lithiums was found to be 2.21 and 2.18 e respectively, which corresponds to a +0.8 charge on lithium (Table II). Thus, it was concluded that the singlet structures of dilithiomethane are as ionic as methyllithium, which has

Table II

	Li electron populations		relative energy (kcal/mole)		
CH_2Li_2 system	Li ISEP[5]	Mulliken[5]	4-31G[3]	6-31G**[5]	DZ+P/CI[4]
singlet					
cis-planar	2.213	2.586	10	7.3	4.2
tetrahedral	2.175	2.605	0	0.0	0.0
triplet					
cis-planar	2.404	2.674	-13	-16.2	5.9
tetrahedral	2.397	2.695	-16	-18.2	4.7

an ISEP value of 2.12 e for lithium, and that they can be represented to good approximation by the ion triplet, $CH_2^{2-}(Li^+)_2$. In contrast to Schleyer's conclusions, only a weak, but distinct, three-center bond was predicted for the planar geometry of singlet dilithiomethane in Streitwieser's analysis of the bonding.

Theoretical predictions about the structure and bonding of dilithiomethane are even further complicated by the possibility that the ground state configuration is a triplet.[10] Since the single determinant Hartree-Fock approximations used in Schleyer's calculations (4-31G) on

dilithiomethane are known to treat triplet states more favorably than singlet states,[11] a more reliable estimate[4] of the relative energies of the four possible states (Table III) was obtained by using a larger basis set (DZ+P) and by including the effects of configuration interaction (CI). Although the singlet tetrahedral state is predicted to be the ground state of dilithiomethane, all four states are remarkably close in energy.

The optimized geometries for the four states (Table III) were calculated with the DZ+P basis set.[4] For the triplet states, the Li-C-Li bond angles are much smaller and the C-Li bond lengths are longer than in the corresponding singlet state. Although the calculated dipole moment for the singlet is large with polarity C^-Li^+ as expected, the triplets are calculated to have an opposite dipole moment with polarity C^+Li^- (Table III). In the multicenter covalent bonding

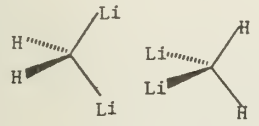
Table III[4]

	angles (degrees)		bond lengths (Å)		dipole moment
CH_2Li_2 system	Li-C-Li	H-C-H	C-Li	C-H	D
singlet					
cis-planar	101.7	102.3	1.844	1.106	4.85
tetrahedral	120.3	107.0	1.981	1.108	5.42
triplet					
cis-planar	73.6	102.9	2.069	1.102	-1.22
tetrahedral	72.4	105.7	2.128	1.101	-0.76

picture of Schleyer, the triplets are formed by removing an electron from a Li-C-Li bonding orbital with π symmetry and placing it into a Li-Li σ bonding orbital. The loss of π bonding in the triplet state thus accounts for the longer C-Li bond lengths, and the increase in Li-Li σ bonding explains the smaller Li-C-Li bond angles. Compared with the singlet states, the electron density projections calculated by Streitwieser for the triplets show a shift in electron density toward the lithiums as well as distinct Li-Li bonding and C-Li antibonding character in the HOMO and subjacent orbital, which also explains the smaller Li-C-Li angles and longer C-Li bond lengths in the triplets. The observed decrease in positive charge on lithium (Table II) and the formation of Li-Li bonding in the triplet states led Streitwieser to the approximation of the triplet tetrahedral state as the summation of triplet methylene and Li_2. The inherent dipole of triplet methylene, which assigns the hydrogens as positive, thus becomes important for the triplet state, resulting in the reversal of the dipole moment of the molecule. Using Mulliken populations, however, the dipole moment of the triplet state is estimated to be 4.48D, compared with the actual value of -1.22D from a direct calculation.[5] This failure of Mulliken analysis to predict even the correct direction of the dipole moment in the

triplet state has thrown considerable doubt on the validity of using Mulliken populations to describe the bonding in dilithiomethane.

Ab initio calculations[12] have been done on a number of possible head-to-tail and head-to-head dimer structures for dilithiomethane using the STO-3G minimal basis set to optimize the geometries. Single point calculations using these optimized geometries and the split-valence basis set 4-31G indicated the head-to-head dimer, **5**, with perpendicular CH_2 groups and four lithiums in a tetrahedral arrangement, to be the energy minimum. The dimerization energy for structure **5** is calculated to be -37 kcal/mole.



5

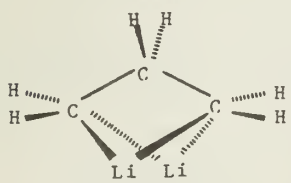
α,ω-Dilithioalkanes

The first α,ω-dilithioalkanes [$Li(CH_2)_nLi$, n = 4-6,10] were synthesized by the reaction [13] of the corresponding dibromoalkane with lithium metal in diethyl ether (eq 5). These stable dilithioalkanes were characterized by reaction with chlorotrimethylsilane.

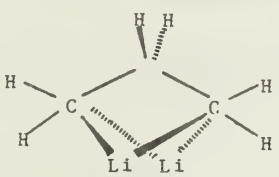
$$Br(CH_2)_nBr \xrightarrow[Et_2O]{\text{Li metal}} Li(CH_2)_nLi \xrightarrow{(CH_3)_3SiCl} (CH_3)_3Si(CH_2)_nSi(CH_3)_3 \qquad (5)$$

A method[14] for synthesizing 1,3-dilithiopropane was developed using indirect transmetallation procedures, but 1,3-dilithiopropane was found to be unstable, undergoing a surprisingly fast β-hydride elimination to give allyllithium and LiH. 1,2-Dilithioethane has yet to be synthesized, but it has been postulated to be an intermediate in the reaction of ethylene and lithium to give vinyllithium.[15]

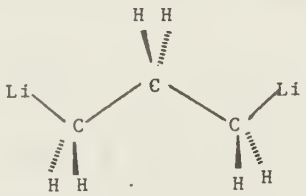
Ab initio calculations[16] at the 3-21G level have found the doubly lithium-bridged structure, **6**, to be the energy minimum for 1,3-dilithiopropane. This bridged structure, the intramolecular equivalent of an alkyllithium dimer, was calculated to be 24.6 kcal/mole more stable than the open form, **8**. To examine the bonding details in the proposed doubly bridged structure of 1,3-dilithiopropane, Schleyer



6



7

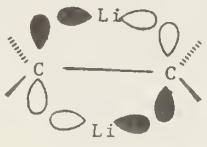


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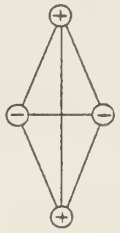
Schleyer calculated the energies of various geometries for the molecule using a 3-12G basis set without the p orbitals on lithium.[16] With this truncated basis set, the energy of structure **6** was raised by 24.0 kcal/mole, which is more than twice the increase in energy (7.9 kcal/mole) calculated for methyllithium. Accordingly, Schleyer concluded that the Li_{2p} orbital contribution to bonding is significant and that multicenter covalent bonding is important in doubly lithium bridged structures (Figure 1a).

Since it is generally accepted[17] that diffuse orbitals are required for adequate description of an anionic carbon, Streitwieser[9] has argued that the very diffuse Li_{2p} orbital is being used as a superposition function to help describe the anionic character of the carbon. Thus, when the Li_{2p} orbitals are omitted, the abnormally large increase in

Figure 1



a) Covalent bonding model for a 1,2-dilithioalkane



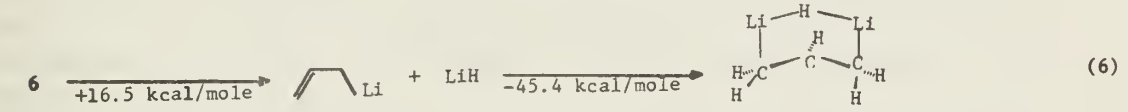
b) Coulombic interactions of point charge model for 1,2-dilithioalkane

energy for **6** is due to inadequate description of the anionic carbon. The alternative model[18] for doubly bridged lithiums proposed by Streitwieser is the ion triplet arrangement (Figure 1b), which emphasizes the electrostatic stabilization due to placing each of the positively charged lithiums near both of the negative carbanion centers. According to Streitwieser, polylithium compounds can be regarded simply as ion multiplets. This type model has been criticized by Schleyer on the basis that it fails to reflect the energy calculations at the 3-21G basis level for 1,3-dilithiopropane.[16] An ion triplet structure for 1,3-dilithiopropane was assumed to have the optimized geometry **7**, where the anionic carbons are sp^2 hybridized and the methylene hydrogens are staggered rather than eclipsed as in **6**. Calculations with the full 3-21G basis set indicated that **6**, for which covalent bonding has been proposed, is 16.7 kcal/mole more stable than the ion triplet model, **7**.

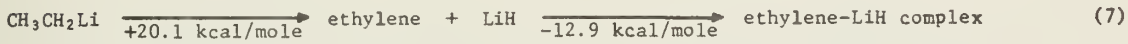
Regardless of whether the bridging in these dilithium compounds is best described by multicenter covalent bonding or an ion triplet model, the formation of a doubly bridged dianion has been used to explain several cases where the second metalation occurs near to the first.[19] X-ray structural determinations have indicated doubly bridged structures

for several 1,4- and 1,2-dilithium compounds.[20] Doubly bridged structures have been proposed for a wide range of dilithium compounds, including dilithioalkenes, dilithioalkynes, and dilithioaryl compounds.[21]

Although solvation and association are very important for organolithium compounds, ab initio calculations on unsolvated monomers are often able to predict experimental behavior quite well.[22] The proposed ground state for 1,3-dilithiopropane, **6**, was calculated[16] to be thermodynamically stable with respect to elimination to produce allyllithium and LiH. This β-hydride elimination was estimated to be endothermic by 16.5 kcal/mole. However, formation of an allyllithium-LiH complex, **9**, was found to be exothermic by 45.4 kcal/mole. Therefore, the extremely facile β-hydride elimination observed for 1,3-dilithiopropane was explained by the overall conversion of **6** to **9**, which is calculated to be exothermic by 29 kcal/mole (eq 6). In contrast, formation of olefin-LiH complexes is much less favorable



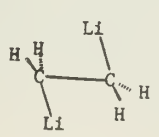
9 (6)



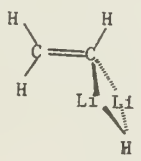
(7)

so that the conversion of ethyllithium to an olefin-Li complex is calculated to be endothermic by 7.2 kcal/mole (eq 7). This agrees with the experimental observation that primary alkyllithiums usually only undergo β-hydride elimination at 100 °C or above.[14]

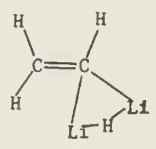
Extensive calculations[23] on the unknown 1,2-dilithioethane predicted that the partially bridged structure **10** has the energetically most favorable geometry. Similar to 1,3-dilithiopropane, **10** is predicted to be unstable relative to the vinyllithium-LiH complex, **11**, by 29.8 kcal/mole. The planar form, **12**, was estimated to be 4 kcal/mole higher in energy than the perpendicular form, **11**.



10

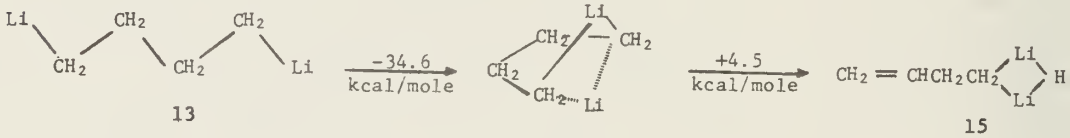


11



12

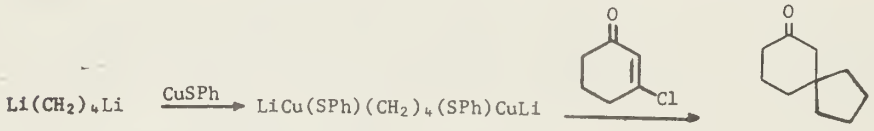
Due to a greater flexibility afforded by the larger ring, the difference in energy (34.6 kcal/mole) between the cyclic form, **14**, and extended form, **13**, of 1,4-dilithiobutane was calculated to be much larger than for the smaller dilithioalkanes.[16] Because of this larger dimerization energy for 1,4-dilithiobutane, the overall process (eq 8) of going from **14** to **15** was calculated to be endothermic by 4.5 kcal/mole, which explains the relative stability of 1,4-dilithiobutane and the higher α,ω-dilithioalkanes.



13 14 15 (8)

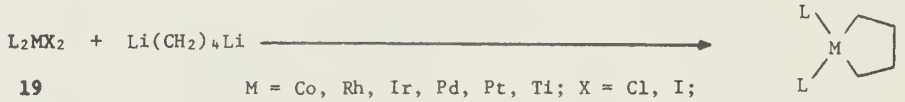
Synthetic uses of dilithioalkanes

1,4-Dilithiobutane and the higher α,ω-dilithioalkanes have been found to be useful synthetic reagents. 1,4-Dilithiobutane, for example, has been used to form the spiroannelating reagent, **16**, which reacts with the chloroenone, **17**, to give the spiroketone, **18**, in 60% yield (eq 9).[24] This single-step spiroannelation method is a valuable alternative to the multi-step sequences usually required to synthesize the spiro[4.5]decane system, which is common to various natural products.



16 17 18 (9)

The reactions (eq 10) of transition metal complexes, L_2MX_2 (**19**), with 1,4-dilithiobutane have been used to synthesize metallocyclopentanes (**20**),[25] which are postulated to be intermediates in the tungsten-catalyzed olefin metathesis reaction.[26]



19 20 (10)

Since dilithiomethane can now be produced in high yield using a modified Ziegler procedure, its use as a synthetic reagent may increase. Some of the derivative chemistry of CH_2Li_2 has already been reported.[27] The reaction of CH_2Li_2 with BR_3 (R = Cl, Br, OCH_3, $N(CH_3)_2$) gives the unstable product $R_2B\text{-}CH_2\text{-}BR_2$, which rearranged to BR_3 and $(RBCH_2)_n$. Chlorotrimethylsilane also reacts with CH_2Li_2 to give $(CH_3)_3Si\text{-}CH_2\text{-}Si(CH_3)_3$ in 88% yield.[27]

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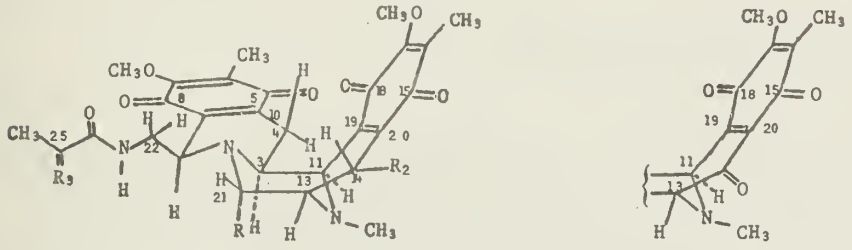
THE CHEMISTRY OF SAFRAMYCINS, ANTITUMOR ANTIBIOTICS

Reported by Greg M. Anstead November 26, 1984

The saframycins are antitumor antibiotics produced in trace amounts by Streptomyces lavendulae.[1] Thus far, 14 saframycin-type antibiotics have been described.[2,3] Their structures are summarized in Figure 1. Although the quinone moiety is found in numerous antibiotics, the presence of two identical quinone units connected by fused nitrogen heterocycles distinguishes the saframycins.[4] This skeletal arrangement is almost unique; aside for the saframycins, it has been found to occur only in antibiotics obtained from the sponge Reniera sp.[5]

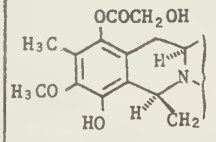
Figure 1

Structures of the known saframycins



letter designation	R	R_2	R_3
A	CN	H	O
B	H	H	O
C	H	OCH_3	O
G	CN	OH	O
H	CN	H	OH, CH_2COCH_3
S	OH	H	O
AH_1 AH_2	CN	H	H, OH
AH_1Ac AH_2Ac	CN	H	H, $OCOCH_3$
AR_3	H	H	H, OH

letter designation	R	R_3
D	H	O
F	CN	O



Rest as in Saframycin A

Saframycin R

Saframycin isolation involved mild basification (pH = 8.0) of the culture broth, followed by $CHCl_3$ extraction. After a series of acid-base partitions, the basic components were separated. In one experiment, 840 L of culture filtrate yielded 8.76 g of the crude base. Repeated column chromatography provided 888 mg of a mixture of saframycins that could be separated by preparative TLC.[1,6,7]

Structure Determination

Although the saframycins were subjected to the whole gamut of spectroscopic techniques,[1] their complexity precluded a detailed structure assignment until an x-ray crystallographic analysis of saframycin C hydrobromide was performed.[8] Unfortunately, its crystal properties did not allow the two possible antipodes to be distinguished. Nevertheless, the x-ray structure of this compound provided sufficient information to rationalize the intricate NMR data which had been collected on several saframycins.[1] Thereupon, the structures of the other saframycins could be assigned by reference to the spectral properties of known members of the series.[9]

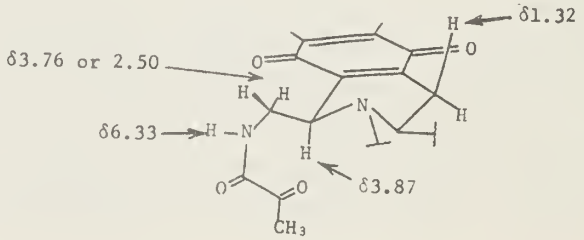
Extensive proton decoupling experiments on saframycins A,C, and R in various solvents verified ^{1}H NMR assignments and provided insight into the conformation of the pyruvate side chain.[9,10] Lown and coworkers[10] found that for saframycin A (saf A) in C_6D_6, deuterium exchange caused loss of the signal at δ6.33 ppm, indicating this was due to the N-H of the side chain. This exchange also caused the two ddd at δ3.76 and 2.50 to collapse to dd; thus, these two protons were located on the side chain methylene carbon.

Irradiation at either δ3.76 or 2.50 simplified the m at δ3.87 to a dd. Irradiation of this signal decoupled the absorptions at δ3.76, 2.50, and 1.32. The latter proton is obviously in a highly shielded region, such as the anisotropic region of the benzoquinone. Its coupling to the proton at δ3.87 is a 5-bond type, necessitating a trans-relationship between the two protons.[11] Therefore, the signal at δ1.32 must arise from the proton adjacent to the benzoquinone on the β-face of the compound. At this point, the assignments can be made and J-values calculated as shown in Figure 2.

Figure 2

Proton NMR assignment for Saf A in C_6D_6 as determined by deuterium exchange and irradiation of signals at δ3.76, 2.50, and 3.87

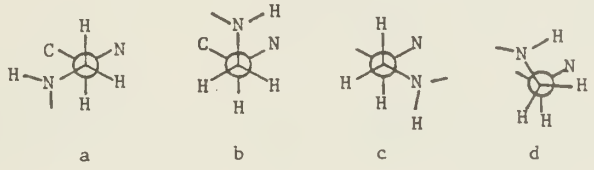
J 6.33,3.75 = 9.5 Hz
J 6.33,2.50 = 4.0
J 2.5,3.76 = 14
J 2.5,3.87 = 4.0
J 3.76,3.87 = 1.5
J 3.87,1.32 = 3.0



Conformer analysis and coupling constants allowed the stereochemical relationship between the protons on C-1 and C-22 to be deduced. The three staggered rotamers that are possible for these two carbons are shown in Figure 3, a-c. The values of $\underline{J}$ 3.76, 3.87 = 1.5 Hz and $\underline{J}$ 2.5, 3.87 = 4.0 Hz preclude a large population of either rotamer a or c, since anti vicinal couplings are generally 9-10 Hz and gauche are 3-4.5 Hz. Further, the dihedral angle between the protons at δ3.76 and 3.87 must be approaching 90°, suggesting the slightly staggered rotamer shown in Figure 3d.

Figure 3

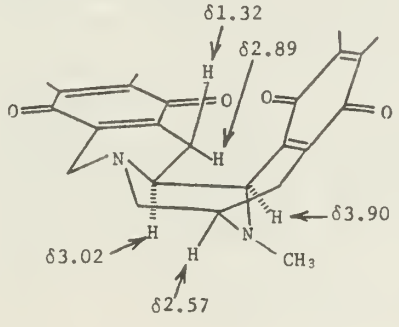
The three possible staggered rotamers for C-1 and C-22 are shown in a-c. The slightly staggered rotamer d is suggested by ^{1}H-NMR coupling data.



With two ring protons assigned, additional decoupling permitted assignment of the remaining ring protons. Irradiation of the aforementioned signal at δ1.32 caused the dd at δ2.89 and the ddd at δ3.02 to simplify to d and dd, respectively. The coupling constants are $\underline{J}$ 1.32, 2.89 = 17.0, $\underline{J}$ 1.32, 3.02 = 11.0, and $\underline{J}$ 2.89, 3.02 = 3.0 Hz. Irradiation at δ3.90 reduces the two ddd at δ3.02 and 2.57 to dd; $\underline{J}$ = 3.0 and 2.5 Hz, respectively. The small magnitude of the latter constant suggests a long-range coupling between the protons at δ3.90 and 2.57. Additional resonances can be designated as shown in Figure 4.

Figure 4

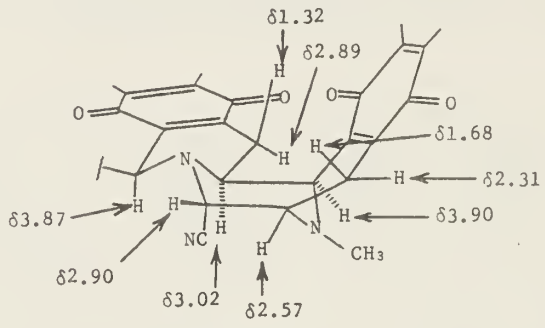
Proton NMR assignments for saf A in C_6D_6 based on decoupling of signals at δ1.32 and 3.90



Irradiation of the dd at δ2.31 reduced the dd at δ1.68 to d and the ddd at 2.57 to dd. Irradiation of the latter signal led to collapse of the d at δ2.90, the ddd at δ3.90, and the two dd at δ1.68 and 2.31. Complete assignment of the ring protons was now possible and is illustrated in Figure 5.

Figure 5

Complete assignment of ring protons for Saf A in C_6D_6



On the basis of coupling constants alone, it is impossible to define unambiguously the stereochemistry of the cyano group. However, the fact that this group undergoes facile elimination in mild acid requires a trans-relationship between the N-lone pair and the nitrile. Thus, the α-orientation is postulated.

Structure Determination of Saframycin R[3,7]

Comparison of the formula of saf R with that of saf A shows the former to have an additional two carbons, four hydrogens, and two oxygens. Proton chemical shifts and coupling constants and ^{13}C spin echo effects demonstrated that both antibiotics possess the same heterocyclic system and side chain. Proton NMR indicated one extra methylene signal at δ4.49 ($CDCl_3$) and two exchangeable -OH groups. The ^{13}C NMR spectrum showed a total of five different carbonyls. The evidence thus pointed to a $-COCH_2OH$ attached to a reduced quinone.

To determine which quinone was reduced, the chemical shifts of the protons adjacent to the two terminal rings were examined in relation to those of saf A. Those ring protons nearest to the amide experienced shifts of 0.1 to 0.2 ppm whereas those adjacent to the other terminal ring shifted less than 0.08 ppm. From these data, it appears that the ring nearest the side chain must be benzenoid.

It remained only to assign the position of the glycolic ester on the hydroquinone. Proton couplings supported the same conformation for the side chain in both saf A and C. This indicated an absence of steric perturbation on the side chain, which would probably occur if the ester were located on the C-8 position. On this basis, the group was placed on C-5.

Total Synthesis[12]

Only one total synthesis of a saframycin has been achieved, that of the (±)-B-form, by Fukuyama and Sachleben. In their convergent approach (see Scheme I), they made imaginative use of α-metallated isocyanides to construct the key intermediate 1, which was then elaborated stereospecifically into the target molecule.

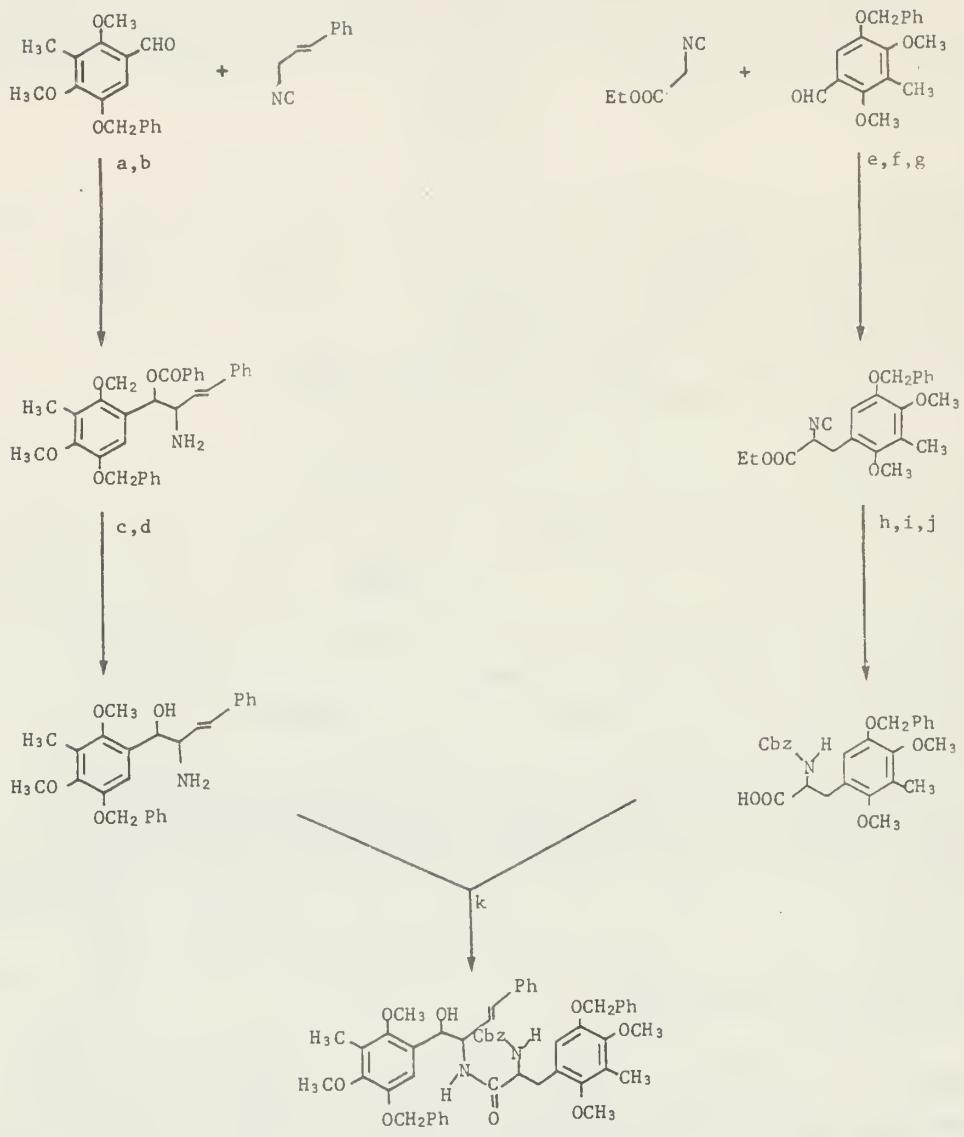
Biological Activity

Takahashi and coworkers compared the antimicrobial spectrum of saframycins A, B, C, and D against 31 test organisms.[1,7] Their results showed that the drugs were most effective against gram-positive bacteria and that the A-form possessed the greatest potency. Nevertheless, it has been demonstrated that certain gram-positive bacteria can reduce saf A to the B, AH_1, AH_2, and AR_3 forms, which are less active.[13,14]

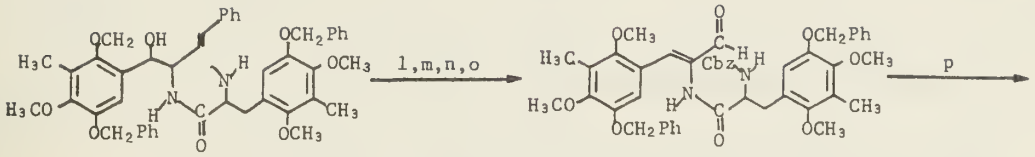
The saframycins have also been tested as antitumor agents. Against L1210 leukemia cells, saframycins having the α-cyanoamino or α-carbinolamine at C-21 showed the greatest cytotoxicity. Introduction of steric bulk at C-14 or C-25 diminished the cytotoxicity. Saframycins which lack either the α-cyanoamine or α-carbinolamine were least effective at growth inhibition.[2]

Against three types of tumors implanted in mice (P388 leukemia, L1210 leukemia, and B16 melanoma), optimized regimens of saf A led to significant increases in lifespan compared with the control group: 119, 83, and 46%, respectively. The R-form produced a 260% increase in life span for mice implanted with the Ehrlich ascites tumor. In addition, saf A appeared to be less immunosuppressive than certain other chemotherapeutic agents, such as adriamycin or carbaziliquinone.[15] Saframycin showed appreciable acute toxicity in mice. The LD_{50} of this compound and saf R were 6 and 30 mg/kg, respectively.[15,7] The C-form showed no toxicity up to 15 mg/kg.[15] The lethal dose for saf A was about 2-6 times the therapeutic dose, while that of the R-form was 4-12 times.[15,7]

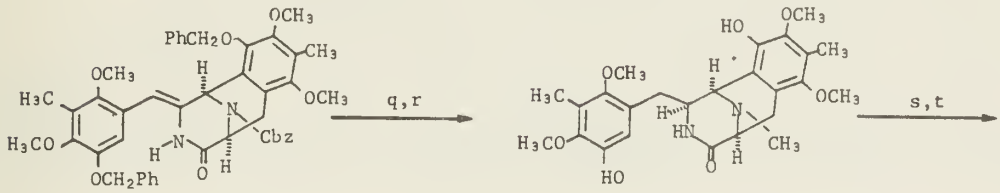
Scheme I

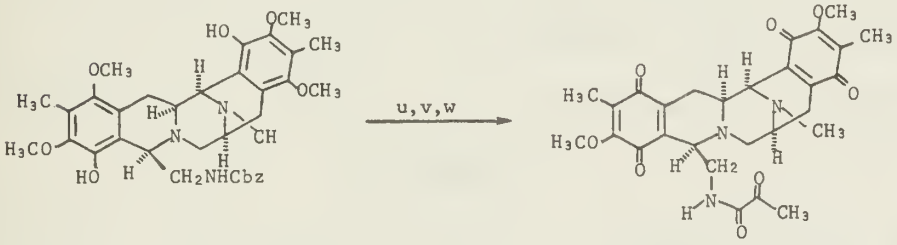


a) n-BuLi; b) PhCOCl; c) 3 N HCl, THF; d) 3 N NaOH; e) KH, THF; f) H_2, Ra-Ni; **g)** $PhCH_2Br$, K_2CO_3, DMF; h) HCl, EtOH; i) CbzCl , $PhNMe_2$, CH_2Cl_2; j) 3 N NaOH; **k)** DCC, CH_2Cl_2



cis and trans





l) Ac_2O, py; m) O_3; n) CH_3SCH_3; o) DBU; p) HCOOH; q) H_2, Ra-Ni, EtOH; r) H_2, Ra-Ni, EtOH, HCHO, H_2O; s) AlH_3, THF; t) $CbzNHCH_2CHO$, CH_3CN; u) H_2, Pd-C, AcOH; v) $CH_3COCOCl$; w) ceric ammonium nitrate

Mode of Action

Ishiguro and coworkers showed that saf A suppressed transcription in L1210 cells.[16] The drug showed preferential binding to duplex DNA or poly(dG)·poly(dC) strands compared with denatured DNA or poly(dA)·poly(dT) or poly(dI)·poly(dA) strands.[17]

Labeled forms of saf A were obtained by growing the streptomycete in the presence of either [^{14}C]-tyrosine or [^{14}C]-NaCN. Incubation of [^{14}C]-try-saf A with DNA and dithiothreitol resulted in increasing amounts of radiolabel associated with the DNA with time. Under identical conditions, [^{14}C]-CN-saf A produced no label incorporation. In the former case, dithiothreitol was necessary to produce isotopic incorporation. In the latter case, dithiothreitol was necessary for loss of radioactivity from saf A. Thus, quinone reduction and loss of CN^- appear to be prerequisites for biological activity.[17]

DNA binding by saf A could be suppressed by adding excess CN^- to the test medium, which indicates that loss of CN^- from saf A is an equilibrium process. This implies that saf S is the active agent of DNA inhibition, via its dehydrated form, an iminium ion. However, the S-form required reduction for maximum binding activity.[17]

Based on the data stated above, the following scenario for inhibition of DNA can be saf A can be postulated. Intracellular reduction of the drug facilitates the loss of CN^- via proton loss by the hydroquinone. The resulting enone imine recyclizes to give an iminium ion. This electrophile reacts with a nearby guanine 2-amino group to form an aminal, which is stabilized by hydrogen bonding between the 8-hydroxy group of the hydroquinone and the 2-keto group of the adjacent cytosine.[2,18]

What accounts for the lesser, though still significant, biological activity of saframycins that lack an α-cyanoamine or α-carbinolamine? In these cases, another mechanism for DNA inhibition must be operative. Lown and coworkers[18] found that saframycins A, C, and R also produced substantial single-strand nicking of DNA under reducing conditions. With analogy to other quinone antibiotics,[4] the initial speculation was that reduced saframycins react with dissolved O_2 to generate reactive species such as H_2O_2, $O_2^{\cdot}$, and $HO^{\cdot}$. This was verified by the fact that the rate of DNA cleavage was slowed by adding catalase, superoxide dismutase, or free-radical scavengers. The

presence of HO· was corroborated by spin trapping and concomitant EPR spectroscopy. The semiquinone of saf C could also be detected in the EPR spectrum.[18]

From the above evidence, the following over-all mechanism was proposed for DNA single strand scission:[18]

1. saframycin + reducing agent $\longrightarrow SH_x$

2. $SH_x + O_2 \longrightarrow SH_{x-1}^{\cdot} + HO_2^{\cdot}$

3. $HO_2^{\cdot} \longrightarrow O_2^{-\cdot} + H^+$

4. $O_2^{-\cdot} + H_2O_2 \longrightarrow HO^{\cdot} + OH^- + O_2$

5. $HO^{\cdot}$ + DNA $\longrightarrow$ single strand breakage

However, the validity of this mechanism in vivo is still a matter of dispute.[18]

In conclusion, the saframycins have posed interesting problems in structure elucidation, synthesis, and biochemical mode of action. Furthermore, their potent antitumor properties may lead to clinical applications.

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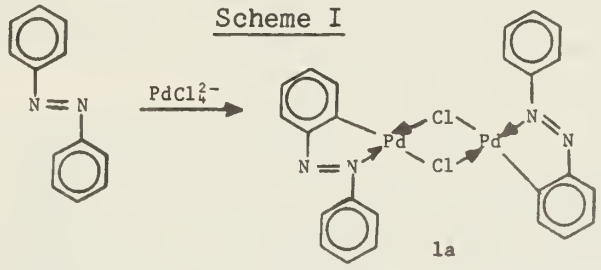
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THE USE OF PALLADIUM METALLOCYCLES IN ORGANIC SYNTHESIS

Reported by Timothy J. Musick November 29, 1984

The first isolation of an aromatic compound with a palladium atom bound to a position ortho to a directing group was reported in 1965.[1] It was found that when palladium chloride was allowed to react with azobenzene in methanol (Scheme I), the dimeric di-μ-chlorobis [o-(phenylazo)phenyl]dipalladium (**1a**) could be isolated in 95% yield. This product is interesting in that a five-member ring metallocycle

Scheme I

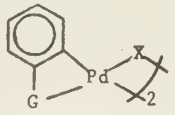


1a

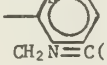
is formed that includes a palladium-carbon sigma bond. This discovery has led to the synthesis of a variety of palladium metallocycles (Table I), all of which contain a heteroatom in the β position of the group ortho to the palladium-carbon bond. Palladium metallocycles have been found to be quite stable species. For instance, cyanide, amine, or phosphine addition to **1a** did not liberate azobenzene as expected, but rather formed new coordination complexes with the metallocycle intact. These new complexes were monomeric in nature, however, which will prove to make them more reactive than the dimeric counterparts.

Table I

Formation of palladium metallocycles



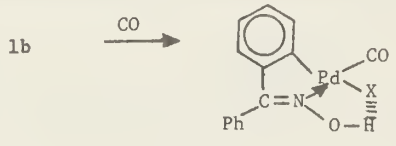
1

No.	G	X	Yield, %	Reference
1a	N=N−Ph	Cl	95	1
1b	PhC=N−OH	Cl	95	2
1c	$CH_2N(Me)_2$	Cl	70	3
1d	CH=N−Ph	Cl	99	4
1e	N=N−Ph	OAc	57	5
1f	CH=N−Ph	OAc	85	5
1g	$CH_2N(Me)_2$	OAc	66	5
1h	S=C−Ph	Cl	61	6
1i	CH_2SCH_3	F_6-acac	-	3
1j		F_6-acac	-	3
1k	$CH_2N{=}C(R)Ph$	OAc	80	5
1ℓ	$CH_3C{=}N{-}N(Me)_2$	OAc	61	5

The formal mechanism for formation of these ortho-palladated species appears to be electrophilic attack on the aryl ring.[7] Prior complexation to the heteroatom may also be involved, but this possibility has not been established due to conflicting data. For example, the coordination compound bis(azobenzene)palladium(II) chloride has been prepared, but it does not react to form the metallocycle[8] under conditions used to form **1a**. Similarly, $(PhCH_2SMe)_2PdCl_2$ does not react with Na_2PdCl_4, while $(PhCh_2NMe_2)_2PdCl_2$ and (1-phenylpyrazole)$_2$ $PdCl_2$ could be cyclometallated by additional Na_2PdCl_4. Therefore, the question of whether these complexes are intermediates in the ortho-palladation reaction has not been answered and may, of course, depend on the individual coordinating species.

Synthetic methodology employing o-palladated species was slow to develop. In fact, the initial conclusion was that they were rather unreactive.[9] The reaction of di-μ-halobis(2,N-dihapto-benzophenone--oxime) dipalladium (II) (**1b**) with carbon monoxide (Scheme II) gave only a different complex with the metallocycle intact and no insertion products. Because palladium-phenyl sigma bonds will normally insert carbon monoxide at atmospheric pressure, the unreactivity of these species was assumed to be due to the high stability of the five-member chelate rings.

Scheme II

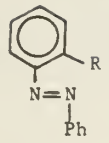


Reaction with Nucleophiles

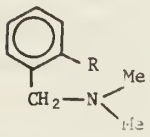
Early work[1] showed that it was possible to effect displacement of the palladium atom with $LiAlD_4$ to form an o-deuterated species. Although this provided hope for success in other nucleophilic reactions, it is neither a convenient nor a practical method of incorporating deuterium into aromatic systems. Fortunately, cyclometallated palladium species have proved to be quite reactive with organolithium compounds and Grignard reagents.[10] A major problem encountered in these reactions is that treatment of a dimeric palladium complex with a nucleophile will produce one equivalent of substituted product and one equivalent of reductive product. For example, treatment of **1a** with methyllithium produces both 2-methylazobenzene (55%) and azobenzene (45%). Other reactions are shown in Table II.

Table II

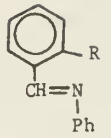
Reactions of dimers with nucleophiles



2a R = H
b R = CH_3
c R = C_6H_5
d R = nC_4H_9



3a R = H
b R = CH_3
c R = $CH_2=CH_2$
d R = C_2H_5
e R = nC_4H_9

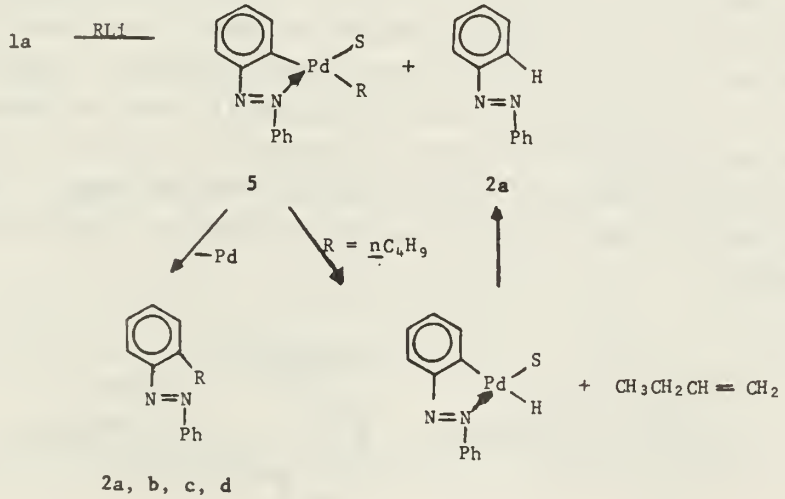


4a R = H
b R = nC_4H_9
c R = CH_3
d R = C_6H_5

Complex	RLi or RMgBr	Substituted Product	Yield, %	Reductive Product	Yield, %
1a	MeLi	2b	55	2a	44
1a	PhLi	2c	42	2a	58
1a	n-C_4H_9Li	2d	5	2a	89
1c	MeLi	3b	49	3a	47
1c	$CH_2=CHMgBr$	3c	44	3a	31
1c	EtMgBr	3d	2	3a	80
1c	n-C_4H_9Li	3e	5	3d	80
1d	n-C_4H_9Li	4b	1	4a	0

These data may be interpreted in terms of the mechanism shown in Scheme III. The first step is nucleophilic substitution of the chloride by the alkyllithium, which then breaks the bridge structure to yield the reductive product **2a** and a complex **5** which can produce the substitution product by reductive coupling. The high yield of reductive product in the case of n-BuLi is presumed to be due to β-elimination of a palladium hydride species, which then forms the reductive product **5a**.

Scheme III



2a, b, c, d

This problem of product mixtures can be overcome by the addition of triphenylphosphine, which is presumed to break up the complexes into monomers. Treatment of o-palladated species with organolithium reagents in the presence of four equivalents of triphenylphosphine gave much greater yields of substitution products (see Table III). As can be

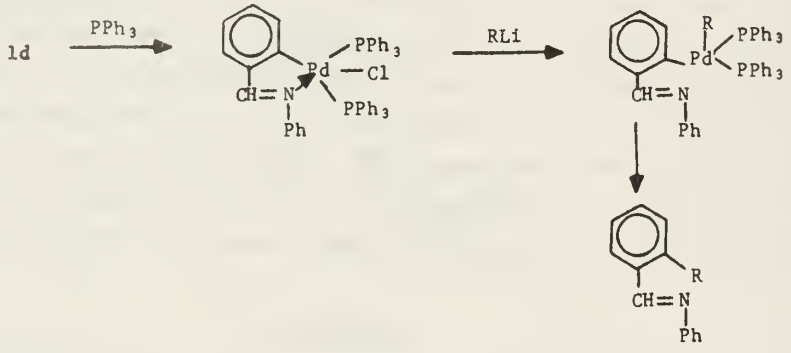
Table III

Reactions with nucleophiles in the presence of triphenylphosphine

Complex	RLi	Substitution Product	Yield, %
1a	MeLi	2b	91
1c	MeLi	3b	99
1d	MeLi	4c	86
1d	n-C_4H_9Li	4b	75
1d	C_6H_5Li	4d	60

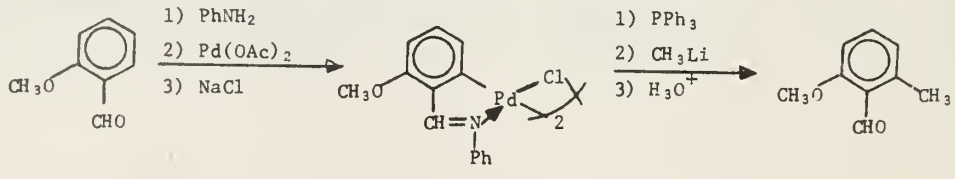
seen, the addition of triphenylphosphine breaks up the palladium dimer and effectively retards the β-elimination of a palladium hydride species from butyllithium adducts to afford good yields of substitution products. The mechanism for reaction of cyclometallated palladium complexes with nucleophiles in the presence of phosphine is shown in Scheme IV.

Scheme IV



Using this methodology, one can effectively produce 2,6-disubstituted benzaldehydes, which are useful but otherwise difficult to synthesize. A modified 2-methoxy-6-methylbenzoyl fragment is a characteristic feature of many biologically active natural products of polyketide origins,[11] but this substitution pattern is usually difficult to establish, with yields in the 50% range. However, using o-palladation, the products can be obtained in 81% overall yield (Scheme V).

Scheme V



Reaction with Olefins

Cyclometallated palladium complexes have also been caused to react quite successfully with olefins in high yields and under mild conditions with complete regioselectivity. A typical reaction is shown in Scheme VI, where the ortho-palladated product of dimethylbenzylamine (**1c**) is treated with an enone to yield the addition product **6** in greater than 90% yield.[12] This reaction appears to be general for enones that do not bear a substituent in the β position (R''=H). Apparently steric effects

Scheme VI

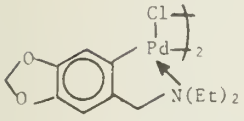
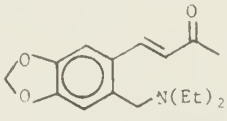


6a-f

limit the substitution pattern. The use of four equivalents of the enone normally provides complete reaction within two hours. This procedure would not be acceptable if the enone were the most valuable unit. However, one equivalent of enone can provide product in roughly the same yield by lengthening the reaction time to 15-20 hours. Results are shown in Table IV.

Table IV

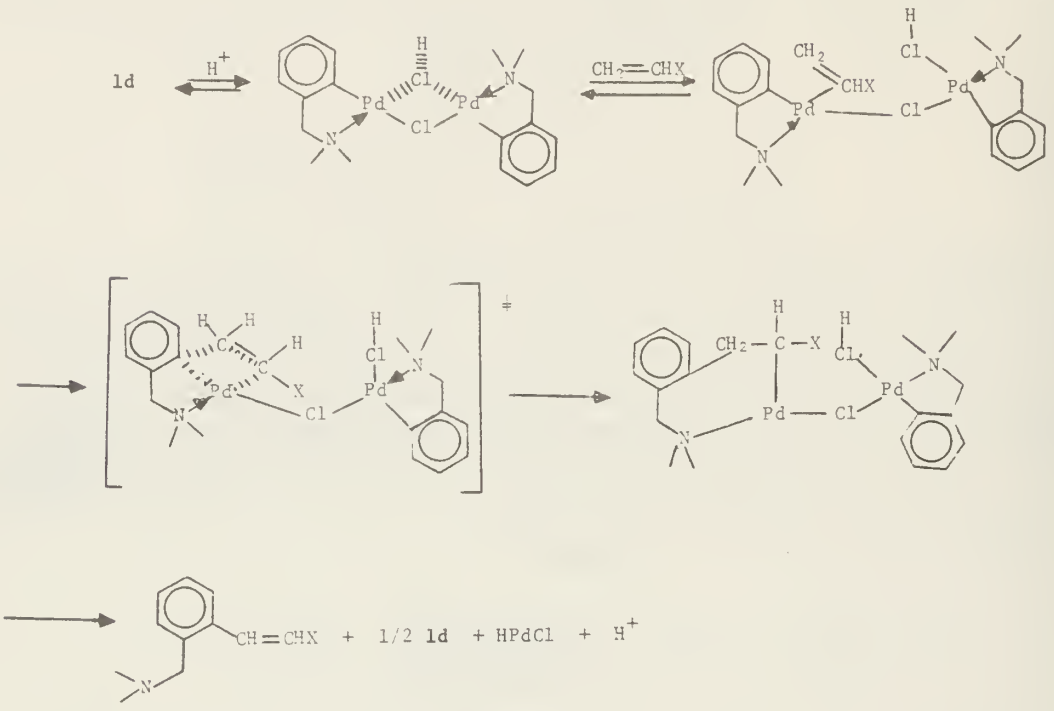
Reaction of palladium metallocycles with enones

Palladium Complex	Enone	Product	R	R'	R''	Yield, %
1c	methyl vinyl ketone	**6a**	Me	H	H	95
1c	ethyl vinyl ketone	**6b**	Et	H	H	93
1c	cyclohexyl vinyl ketone	**6c**	cyclo-C_6H_{11}	H	H	96
1c	phenyl vinyl ketone	**6d**	ph	H	H	94
1c	3-penten-2-one	**6e**	Me	H	Me	0
1c	3-phenyl-3-buten-2-one	**6f**	Me	Ph	H	80
	methyl vinyl ketone					95

Reactions of ortho-palladated species with olefins such as styrene show a positive salt effect.[13] That is, the reaction is greatly accelerated by the addition of $NaClO_4$ or $LiClO_4$. This is viewed as evidence for polar transition states or intermediates. The reaction is also accelerated by the presence of acids such as CH_3COOH or $HClO_4$. The mechanism has been studied in depth[14] in the hope that it can provide relevance to the arylation of olefins with palladium catalysts and other palladium catalyzed reactions. It is known that unstable aryl palladium

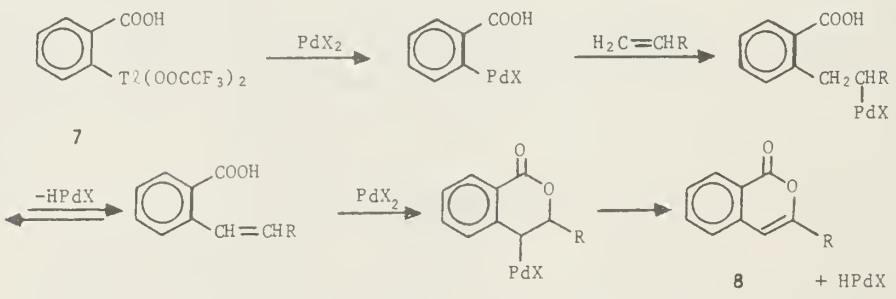
intermediates are formed in these reactions, and it is hoped that the ortho-palladated aromatic compounds will provide a good model. The formal mechanism that has been developed is shown in Scheme VII, using dimethylbenzylamine as the aromatic substrate.

Scheme VII



A variant of the methodology has been used in the synthesis of a number of biologically important isocoumarins (Scheme VIII).[15] Ortho-thallated benzoic acid (**7**) was treated with a palladium salt to form, presumably, the ortho-palladated intermediate, which then reacted with an olefin and cyclized to form 3-alkylisocoumarins (**8**) in reasonable yield (41-80%).

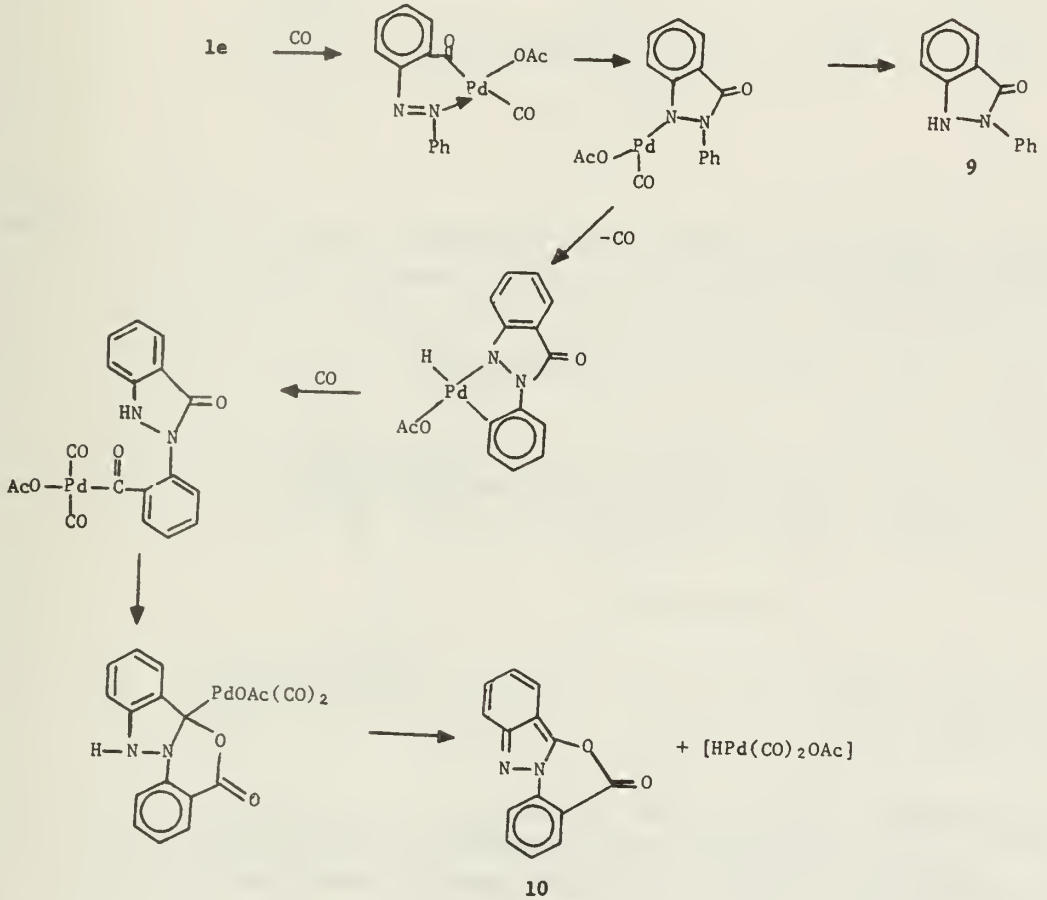
Scheme VIII



Carbonylation Reactions

Perhaps the most promising synthetic applications of ortho-palladation products involve insertion of carbon monoxide into the palladium-carbon bond. This technique has been used to synthesize a variety of unusual heterocyclic compounds. Heck[5] found that metallocycles derived from palladium acetate had better solubility properties, higher reaction rates, and gave higher yields of carbonylated products. In general, the optimum reaction conditions are at 100°C and 150 atmospheres. Reactions can occur at room temperature and 40 psi, however. The carbonylation of **1e** (Scheme IX) yielded 2-phenyl-1H-indazolone (**9**) (44%) and the diazalactone **10** (15%). If this reaction was carried out in ethanol, other products could be isolated

Scheme IX

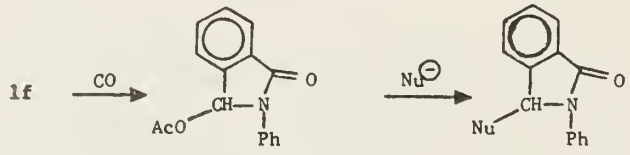


due to ethanolysis of various intermediates. The tendency for azobenzene to react at both aromatic rings complicates the carbonylation reaction to a large extent. If one of the phenyl rings were to be blocked in the ortho position, then higher yields of the biologically active indazolones might be obtained. Conversely, the lactone **10** has

been used to synthesize the so-called antibimanes,[16] which themselves have biological use.

The carbonylation of imine ortho-palladated species (**1f**) was more straightforward (Scheme X). Formation of only one product, 3-acetoxy-3-phenylphthalimidine (**11**) was observed in over 65% yield. Moreover, if the reaction was run in the presence of a nucleophile, incorporation into the product was observed. This then appears to be the most useful of the carbonylation reactions. Carbonylation of tertiary benzylamine complexes (**1g**) produced some unusual results (Scheme XI). The major

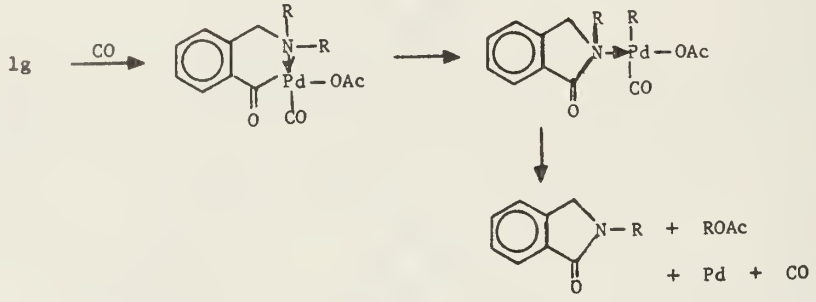
Scheme X



11

product isolated was a phthalimidine produced by cyclization and loss of one of the N-alkyl groups. The yields were over 70%.

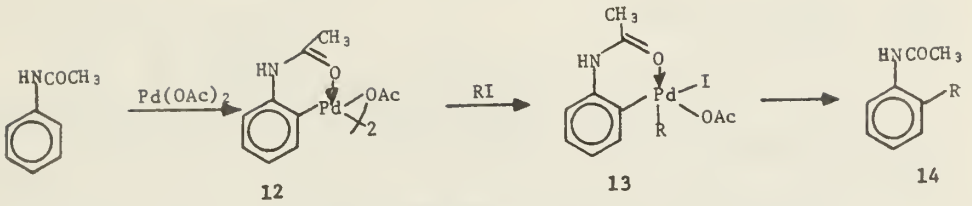
Scheme XI



Reaction with Electrophiles

The versatility of palladium metallocycles in synthetic transformations is shown by their reaction with electrophiles. Palladated acetanilide (**12**) plus alkyl halides can produce the ortho-alkyl product (**14**) in yields up to 81% (Scheme XII).[17] This reaction is believed to proceed by oxidative addition to form a Pd(IV) intermediate (**13**). An interesting synthetic application of the

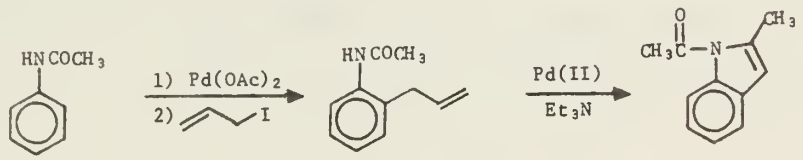
Scheme XII



12 13 14

technology involved the use of allyl iodide as the electrophile, followed by heating in triethylamine to produce N-acetyl-2-methylindole (**15**) (23% overall yield) (Scheme XIII).

Scheme XIII



76% 15

It has become clear that palladium metallocycles are quite useful and diverse in their synthetic applications, capable of reacting with nucleophiles, olefins, electrophiles, and carbon monoxide to produce a variety of substituted or heterocyclic systems, some of which are known to be biologically active. This reaction is quite tolerant of other functional groups located in the molecule. A severe limitation is the reactivity of palladium compounds with olefins, which makes complex olefin-containing systems unaccessible by this technique.

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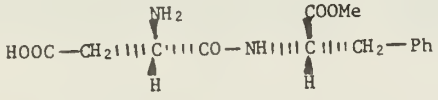
THE DESIGN OF DIPEPTIDE SWEETENERS: ASPARTAME AND ITS DERIVATIVES

Reported by Susan Sondej Pochapsky December 6, 1984

Since the discovery of saccharin in 1879,[1] there has been an ongoing search for new, potent sweetening agents. Approximately thirty different classes of sweet molecules are known today; however, only a handful of these are suitable as sweeteners in food and beverage applications, since most of the agents do not meet the four necessary requirements:[2]

1) The sweetener must be safe for human consumption.
2) All side tastes should be absent and the persistence of sweetness should be close to that of sucrose.
3) The sweetener should be sufficiently soluble and stable at elevated temperature. In addition, since carbonated beverages are one of the major uses, acid stability is required.
4) The sweetener must be economical to synthesize on an industrial scale.

In 1965, L-α-aspartyl-L-phenylalanine methyl ester (APM; aspartame **1**) was discovered to be 180 times as sweet as sucrose.[3] Since that time, APM has been approved by the FDA for use in food and beverages, and much research is continuing in this area, in an effort to decrease production costs and increase the potency of the sweetener.



1

Synthesis

Classical peptide synthesis techniques involving protected amino acids, activating groups and subsequent de-protection, were not suitable for industrial production of APM. A more useful synthetic method was introduced which did not require expensive reagents or protecting groups and provided reasonable yields.[4] This process combined a salt of L-aspartic anhydride with a strong acid like benzenesulfonic acid, followed by addition of L-phenylalanine methyl ester. Both α- and β-dipeptides are formed, but the α-isomer can be selectively recrystallized to give 33% yield overall. A further modification consists of allowing a N-protected aspartic acid anhydride to react with L-phenylalanine methyl ester, followed by removal of the N-protective

group.[5] Since this process uses water as the solvent it has a considerable cost advantage. Also, typical linkage efficiencies of the two amino acids are greater than 95%, and an α-isomer selectivity of 90% is observed. Since all of the classical methods result in some formation of β-dipeptide and some even have other by-products such as di-esters (at Asp-COOH and Phe-COOH) or mono-esters only at the Asp-residue carboxyl group, on an industrial scale, there is a lot of material that is useless.

Some of the newer enzymic methods may eventually eliminate this waste. One current enzymic process combines L-aspartyl-L-phenylalanine and a methanol/water mixture, followed by addition of Subtilisin Carlsberg (a serine alkaline protease which acts on aromatic amino acids selectively), to produce selectively APM.[6] Other processes are aimed towards using an enzyme to do the actual coupling of the amino acids.[7] Still more work in this area is necessary to determine whether or not there is a significant cost advantage over some of the modified chemical procedures.

With the advent of genetic engineering, another possibility has arisen. A proposal has been made to produce an alternating polypeptide of phenylalanine and aspartic acid, which can then be hydrolyzed and chemically methylated to produce APM.[8] This method would allow the use of inexpensive, racemic mixtures of raw materials rather than pure L-amino acids.

A further cost reduction would be to discover an analog of APM which is much more potent, thereby reducing the cost-per-sweetness.

Design of a Sweetener

Taste response to a stimulus can be described in terms of the four primary tastes: sweet, sour, salty and bitter. The goal in sweetener design is to minimize all side tastes while maximizing sweetness. In addition, it would be desirable to develop a method for reliable prediction of the biological activity of a potential sweetener without the expenditure of time and money necessary for actual synthesis and biological screening. These goals are in fact identical to those in drug design, and most of the principles described here have been adapted from that body of research.

In an effort to gain some information concerning the structural requirements necessary for sweetness, Shallenberger and Acree analyzed a wide variety of known sweet molecules and found that all of them

contained an A-H/B binding unit, where A and B are electronegative atoms separated by 2.5-4.0 A, and H is a hydrogen atom. They proposed that this system from the sweet molecule forms hydrogen bonds with a complementary A-H/B system from the receptor, and it is this interaction that is the basis of sweet taste.[9] Based on examination of the stereochemistry of sweet molecules, Kier has further modified the description of a sweet molecule.[10] He proposes that the receptor must be stereoselective, since frequently one enantiomer is sweet, while the other is not. This would indicate an additional important binding site, as chiral recognition requires at least three interactions (at least one of which must be stereochemically dependent).

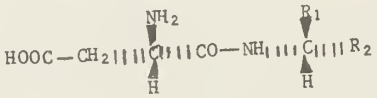
It is at this point where the validity of general conclusions about sweet molecules becomes questionable. Currently, more specific conclusions about necessary structural requirements for sweetness can only be made within a particular class of sweeteners. The reasons for this will be discussed in the last section of this review.

With these basic concepts as a starting point, the design of a dipeptide sweetener is most easily attempted by the QSAR (quantitative structure-activity relationship) approach. This approach assumes that the biological effect of a stimulant molecule is dependent on the size, shape, polarity, and functionality of that molecule. The QSAR approach consists of choosing molecular parameters that will adequately describe each of these qualities and developing a mathematical expression relating these parameters to the biological response. A typical correlation equation is shown, where C is the concentration necessary to induce a particular biological effect, π is the Hansch parameter for hydrophobicity, σ is the Hammett parameter for electrostatic character, and E_s is the Taft parameter for steric character. The coefficients a, b, c and d were determined by least-squares multiple regression analysis.[11]

$$\log (1/C) = a + b\pi + cE_s + d\sigma$$

For the last fifteen years, researchers have been evaluating sweet dipeptides and deducing qualitative relationships between structure and activity. All of the studies found that although the phenylalanine moiety could be altered substantially, the L-aspartic acid moiety was a necessity. The only acceptable substitution (with retention of sweetness) for L-aspartic acid is aminomalonic acid.[12] The general structure of a sweet dipeptide was found to be **2**, where R_1 is a small, hydrophobic group (carbomethoxy in APM) and R_2 is hydrophobic and

larger than R_1 (benzyl in APM).[13] By synthesizing many derivatives of this general form, it was discovered that the sweetness decreased as the size and hydrophobicity of R_1 increased. In addition, the intensity of sweetness was the greatest when R_1 and R_2 were very different in size.[14] Therefore, L-phenylalanine could be replaced by a D-amino acid, if the sizes of the two substituents were correct. One example, D-alanine n-propyl ester where R_1 is the methyl group and R_2 is the ester moiety, was found to be 125 times as sweet as sucrose.[13]

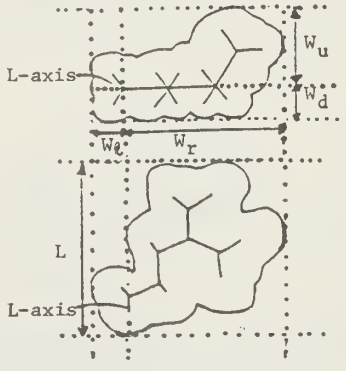


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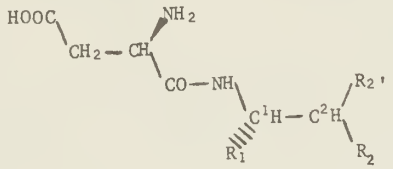
It has only been recently that a quantitative evaluation has been performed. Iwamura used data obtained by four different research groups to develop his mathematical correlation.[15] His choice of hydrophobic parameter was π, which was estimated for the part of the molecule substituted on the common aspartylamino moiety, and the values were taken from, or estimated from, the literature.[16,17] The chosen electronic parameter, σ^*, was also estimated only for the structure substituted on the common aspartylamino moiety. Again, values were obtained from the literature.[16,18] Iwamura's choice for the steric parameter is interesting because instead of the typical one-term description of the steric effect, he uses five different length and width parameters. This should provide a more accurate description of the shape and size of the molecule and hopefully, allow a more accurate correlation to be obtained. The steric parameters were calculated by the STERIMOL program[19] and are shown in Figure 1, where they are used to describe a 4-methylamyl substituent.

Figure 1

Steric parameters for 4-methylamyl substituent



The length of a substituent along the bond axis connecting that substituent to the rest of the molecule is defined as L. The W_r parameter is the width in the direction in which the longest chain of the substituent extends in the staggered form. W_ℓ is the width in the direction opposite to that of W_r. The W_u and W_d parameters are widths upward and downward, when viewing the substituent from the connecting end along L with W_r to the right.



3

Using biological data[13,20-23] and literature values for the chosen parameters, thirty-nine different sweet molecules with the general structure shown (3) were used to obtain the linear regression equation.

$$\log SP = 0.66\sigma^*(\pm 0.25) - 1.06InA\ (\pm 0.26) + 0.78(W_u)_1\ (\pm 0.41) + 0.24(W_u)_2\ (\pm 0.18) + 1.20(W_r)_2\ (\pm 1.16) - 0.15[(W_r)_2]^2\ (\pm 0.13) - 2.85$$

The indicator variable, InA, was necessary as a correction for biological data from different laboratories. The sweetness potency, SP, is measured relative to that of sucrose on a mole/mole basis. Various statistical tests were performed to determine whether or not the equation was statistically significant. The multiple correlation coefficient, r, was found to be 0.92, indicating that 85% (r^2) of the variance in the log SP data was explained by the equation. Also, the standard deviation of the observed log SP values from those calculated, s, was determined to be 0.28.

Statistically, the equation seemed to provide a good description of the structural requirements necessary for sweetness. Iwamura then used this equation to calculate log SP values for twenty-five different compounds which had previously been evaluated qualitatively (i.e. sweet, bitter and tasteless).[20,21] His predictions were reasonably accurate with the less sweet molecules having small log SP values. However, many bitter compounds had fairly large sweet potency values. This is not unreasonable, as none of the four primary tastes are mutually exclusive. Perhaps these molecules interact with both sweet and bitter receptors and the bitter taste masks the sweet taste. Consequently, Iwamura's equation cannot be used to predict whether or not a molecule will be sweet. However, by maximizing the log SP value by manipulation of the molecular parameters used in the equation, the potency of a molecule can be accurately predicted, thereby allowing an increased

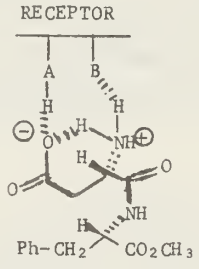
number of very potent sweeteners to be synthesized while decreasing the synthesis of marginally sweet molecules.

Mechanism of Action

It is desirable to determine the nature of the sweet taste receptor because this would allow more efficient predictions of potential sweet molecules. Currently, it is believed that the series of events leading to the neurotransmission of a sweet taste response are those that follow.[24] A molecule with the appropriate molecular characteristics (size, functionality, shape, and hydrophobicity) complexes in a very specific manner with a proteinaceous component of the plasma membrane of a receptor cell. Figure 2 provides a schematic representation of this complexation.[14] Since within the pH range of 4-9, the dipeptide esters will exist in a zwitterionic form,[25] it is believed that this intramolecular interaction will persist and participate directly with the A-H/B system of the receptor as shown. Upon complexation, this component undergoes a conformational change which results in a change in the electrical potential of the cell membrane. The chain of events leading from this change in potential to neurotransmitter release is under investigation.

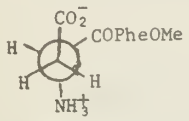
Figure 2

Proposed interaction between receptor and APM

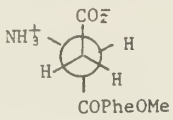


Of course, an accurate description of the receptor site would enhance understanding of the interactions which are occurring, and currently two approaches are being taken. The biological approach consists of isolating the sweet-sensitive protein from bovine and canine tongues. Several researchers have claimed to have isolated the active component[26] but their data and conclusions have been challenged.[24] The chemical approach consists of using the structural characteristics of sweet molecules to determine the geometry of the receptor site. Temussi attempted to determine the topography of the receptor by predicting the active conformation of aspartame and then defining the receptor site as a cleft in the protein, limited by the van der Waals radii of the active conformation.[27] He used proton nmr and potential energy data to

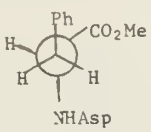
calculate the fractional populations of the nine possible conformers (F_ID_I,...$F_{III}D_{III}$; based on severable reasonable assumptions) of aspartame. The four major conformers were determined (F_ID_{II} > $F_{II}D_{II}$ >



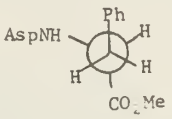
D_I



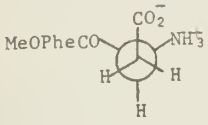
D_{II}



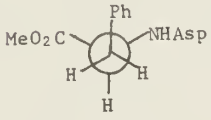
F_I



F_{II}



D_{III}



F_{III}

F_ID_{III} > F_ID_I) and each was judged on its likelihood of being the active conformation. Temussi ruled out F_ID_I because the carboxyl and amino groups were trans, which would violate Shallenberger's A-H/B theory.[9] Assuming that the phenylalanine sidechain would interfere sterically with the interaction between receptor and A-H/B moiety, Temussi also discarded F_ID_{III}. The $F_{II}D_{II}$ conformer was eliminated because it was inconsistent with Shallenberger's "spatial barrier" theory,[28] leaving F_ID_{II} as the active conformation. Unfortunately, Temussi's conclusions can be questioned at several points. First, and probably most important, there is no theoretical basis for assuming that the conformation of aspartame involved in receptor binding must be a significantly populated one in solution. Only the rate of receptor-substrate interaction should be affected by the population of the active conformer. In addition, the reasons for omitting F_ID_{III} and $F_{II}D_{II}$ as possible active conformations are questionable.[14] Since the steric limitations of the receptor are not known, it cannot be assumed that the phenylalanine sidechain will interfere with the hydrogen bonding interaction of substrate and receptor in conformer F_ID_{III}. Also, Shallenberger's "spatial barrier" theory which was invoked to eliminate $F_{II}D_{II}$ is purely hypothetical, and in fact, is not the only proposed theory to account for the interactions at that end of the dipeptide. Further evidence in favor of Temussi's active conformation description might be obtained by synthesizing rigid analogues of the proposed active conformer. If this theory is accurate, it is expected that a molecule forced to remain in the active form would be a much more potent sweetening agent.

In addition to the difficulties in determining the receptor topography, there is much controversy concerning the number of

sweet-taste receptors. Many researchers, as a result of the wide variety of sweet molecules, have proposed multiple sweet receptors, each being specific for a class of sweeteners.[29,30] This conclusion seems unlikely and, if true, would make further progress in sweetener design very difficult.

Fischer has provided an alternative explanation.[31] He proposes that, initially, a sweet molecule is attracted to an α-helical portion of a protein. As a result of the receptor-substrate interaction, the protein undergoes transition to a β-pleated sheet conformation. Once the sweet molecule dissociates, the protein can relax to the original α-helical form. Fischer believes that the driving force for the conformational change of the receptor protein could be due to disruption of the stabilizing side chain interactions of the α-helical form by the sweet molecule, stimulating the change to a β-pleated sheet. This proposal is very attractive, as it explains the wide variety of sweet molecules which exhibit the same biological response. Each different class of sweeteners can interact with a particular residue on the α-helix and induce the same change to the β-pleated sheet. Unfortunately, experimental proof of this proposal has not yet been obtained.

In summary, there is research still to be done in the field of sweetener design. The prediction of more potent potential sweeteners within a particular class of compounds, using the QSAR approach, seems very promising. One of the main sources of error in this approach is the variability of the biological data. Currently, there is no instrumental way to quantify sweetness, and the biological data are obtained from taste panels.[14] This method provides fairly reliable information within a given laboratory, but comparisons between different laboratories sometimes result in significant discrepancies. Further research in the area of sweet-sensitive protein isolation may eliminate these problems. If the receptor protein can be isolated, in vitro studies would allow extensive research on the interaction between receptor and sweet molecule, potentially producing a means of determining sweetness objectively.

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1984-85, Semester II

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Semester II, 1985

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RECENT ADVANCES IN BIOMIMETIC CHEMISTRY

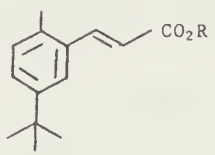
Reported by Andrew L. Staley January 28, 1985

"Biomimetic chemistry" is a term coined by Breslow[1] to describe a relatively new subdiscipline of organic chemistry. There are three general approaches to the study of biomimetic chemistry. First, there has been extensive effort in recent years to design and produce "synthetic enzymes": simple compounds that exhibit catalytic, or at least rate-enhancing, properties that are similar to those of biological enzymes. Second, biosynthetic chemists are generally interested in the enzymatic pathways and intermediates involved in the production of various natural products. The in-vitro synthesis of a putative intermediate from a proven intermediate (or vice-versa) can lend support for its inclusion along the hypothetical pathway. Third, the sequential in-vitro conversions of biological compounds under carefully defined conditions can provide evidence for a particular type of enzymatic mechanism.

Perhaps the best studied artificial enzyme system is the cyclodextrins.[2] These compounds are doughnut-shaped rings constructed from six, seven or eight glucose residues (alpha, beta and gamma cyclodextrins, respectively). The cyclodextrins are water soluble due to the hydroxyl groups of glucose on the exterior, but their interiors (which have the dimensions of 7 Å depth by 5, 7, or 9 Å width) are hydrophobic.[3] The cyclodextrins can therefore bind hydrophobic molecules in their interiors, which in turn can lead to a change in the susceptibility of those molecules to certain reaction conditions.

The cyclodextrins have been used effectively in the modelling of several enzyme systems. Transaminase (which catalyzes the exchange of an amine group from an amino acid to a keto acid), chlorinase (which catalyzes the chlorination of aromatic rings), and ribonuclease (which cleaves RNA) have all been modelled by the covalent attachment of the appropriate cofactors to the cyclodextrin ring. The general observations from these "rationally designed" systems are increased rates of reaction, higher regio- and stereoselectivity, and milder reaction conditions than the corresponding "free solution" reaction (see reference 3 for a review).

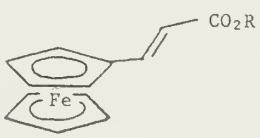
Breslow has had moderate success in applying cyclodextrins as models for the serine transacetylases, such as chymotrypsin. This enzyme catalyzes the hydrolysis of peptide bonds by first forming an intermediate ester linkage between the hydroxyl group of a serine residue and the acyl carbonyl of the attacked amide linkage. Subsequent hydrolysis of the serine ester regenerates the free enzyme and releases the cleaved peptide. The cyclodextrin models have been able to perform the first but not the second step, and therefore are not true "enzymes". However, a significant rate increase has been observed for the hydrolysis of the p-nitrophenol esters of the cinnamic acid **1**, adamantylpropiolic acid **2**, and ferrocenylacrylic acids **3** and **4** (on the order of 750, 15,000, 750,000, and 3 x 10^6 times faster, respectively, compared to the "free solution" hydrolysis in water at the same pH).[4] The rate increases are attributable



1



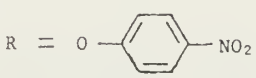
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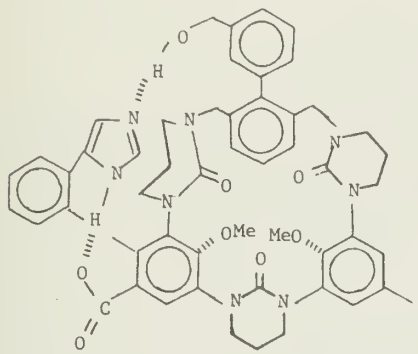
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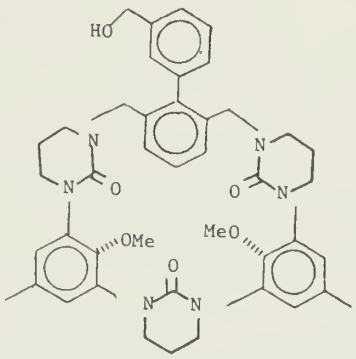
to the formation of a stable complex between the substrates and the cyclodextrin interior (enthalpic factor), and the subsequent attack of a closely situated hydroxyl group on the exterior (entropic factor).

Cram and his coworkers have provided an elegant approach to a "synthetic" transacetylase. Based upon information derived from crystallographic studies of chymotrypsin and the use of molecular models, the workers were able to devise a "reactive

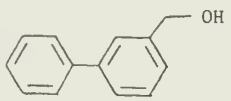
site" **5** that contained all the requisite characteristics of the natural enzyme in the proper orientation: a binding site (or cavity), an hydroxymethylene (the nucleophile), and imidazole and carboxyl groups (the proton transfer mechanism). To date, however, the total synthesis of **5** has not been reported, but the model compound **6** has been studied. Like the cyclodextrin models, **6** is not a true catalyst in that the modified substrate is not released (i.e., no catalytic turnover).



5



6



7

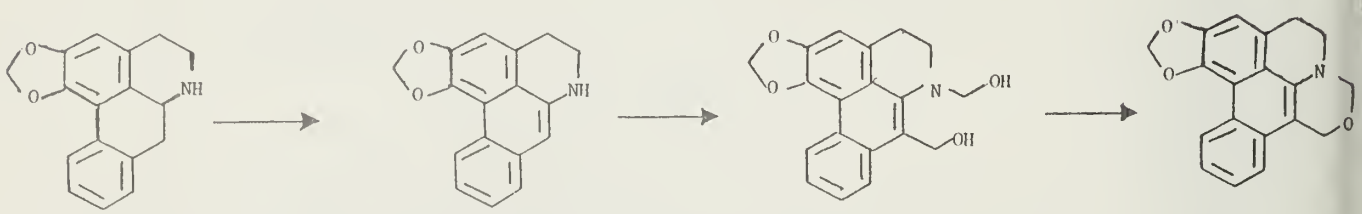
The hydrolysis of the perchlorate salts of the p-nitrophenol ester of alanine ($ClO_4 \cdot NH_3CH(CH_3)CO_2 \cdot pNP$) in $CDCl_3$ saturated with D_2O has been studied using the host **6**. Rate enhancements on the order of 10^{11} have been observed relative to hydrolysis mediated by the non-complexing reagent **7**.[5a] Like the cyclodextrins, this rate enhancement is attributable to the favorable (enthalpic) complexation of the substrate within the "reaction center" of the host. An added benefit with Cram's model is what he has termed "preorganization": the favorable collection and orientation of all reactive groups before complexation occurs. That is, complexation leads to a consistently defined orientation in which the reaction transition state is favored over any other possible coordinate.

There has been an exchange of statements between Breslow and Cram regarding the rate enhancements observed with their

enzyme models (10^8 and 10^{11} respectively).[6a] The results and observations of both researchers are valid and real, but significant differences in their approaches must be kept in mind. Breslow's cyclodextrins catalyze an aqueous acylation reaction, and the standard kinetic rate is based on aqueous hydrolysis of an appropriate ester in alkali (pseudo-first order rate constant). Cram's synthetic enzyme catalyzes the same type of acylation in an organic medium, with the standard hydrolysis rate based on the intermolecular (i.e., second order rate constant) reaction using alcohol **7**. The two approaches nonetheless yield the same kind of result.[6b] The main difference arises from the magnitude of the binding constants relative to the kinetic constants. The cyclodextrins have a low binding constant (10^2) and high intramolecular reaction rates (10^6), while the synthetic hosts have high binding constants (10^8) and low intracomplex kinetic rates (10^3). However, the issue is still open to discussion.

A few synthetic sequences of interest to biosynthetic chemists can be found in the recent literature. Lenz and Koszyk[7] have demonstrated a biomimetic synthesis of the alkaloid duguenaine (**8**) by a method that parallels its proposed biogenesis from the noraporphine alkaloid anonaine (**9**). The important reaction is an enamide-like condensation of two formaldehyde molecules to dehydroanonaine (**10**). Treatment of **10** with

Equation 1

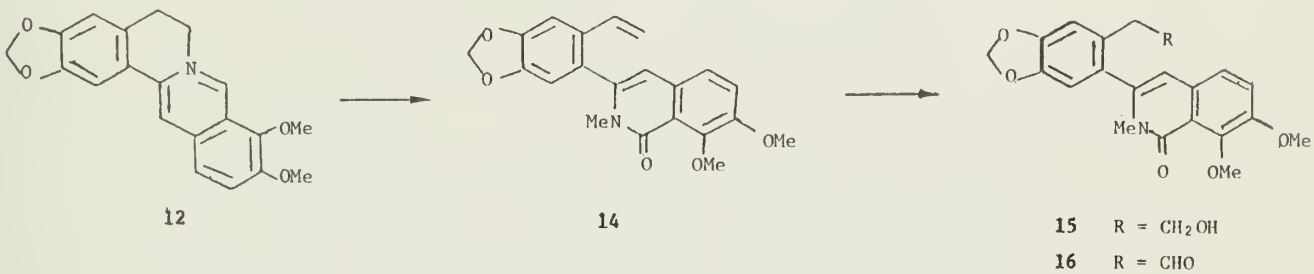


9 **10** **11** **8**

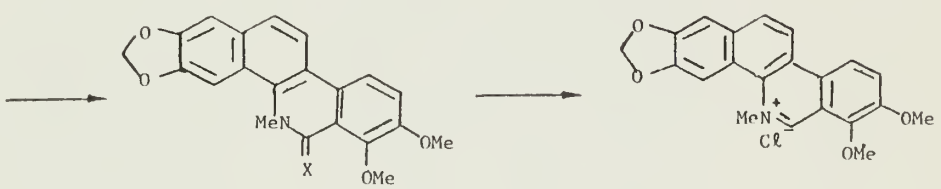
aqueous formaldehyde for 24 hours at room temperature leads directly to duguenaine in 76% yield, presumably via the bismethylol compound **11**.

A clean biomimetic transformation of the alkaloid berberine (**12**) into chelerythrin chloride (**13**) was reported by Hanaoka et al.[8] The synthesis of enamide **14** from **12**[9] permitted the hydroboration to alcohol **15**. The phenanthridine **17** was isolated directly after oxidation of **15** with pyridinium chlorochromate, presumably through the aldehyde **16** as in the reported biosynthetic pathway.[10] Reduction of **17** with $LiAlH_4$ to alcohol **18**, followed by dehydration in HCl, provided **13** in 45% overall yield from **14**.

Equation 2



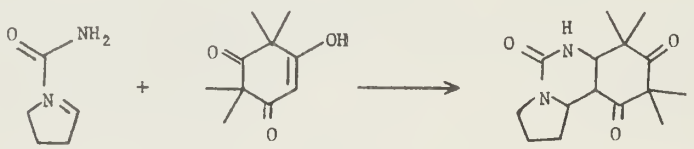
12 **14** **15** R = CH_2OH; **16** R = CHO



17 X = O; **18** X = OH,H **13**

Clardy and Okamoto have reported a biomimetic synthesis of the novel Uvaria metabolite syncarpurea (**19**).[11] Syncarpic acid (**20**), isolable from the same species, had been synthesized from 2,4,6-trihydroxyacetophenone by an established preparation.[12] 1-Carboxamido-Δ^1-pyrrolinium ion (**21**) was derived from citrulline by reaction with N-bromosuccinimide and removal of HBr. Addition of **20** to a methanol-water-HCl solution of **21**, stirring at room temperature for 48 hours, and then open air oxidation provided **19** in 53% yield.

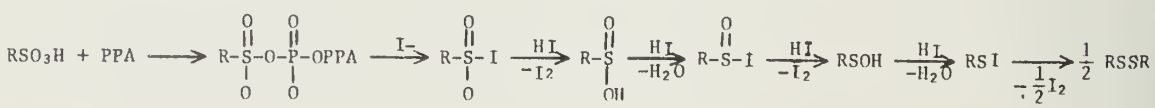
Equation 3



21 **20** **19**

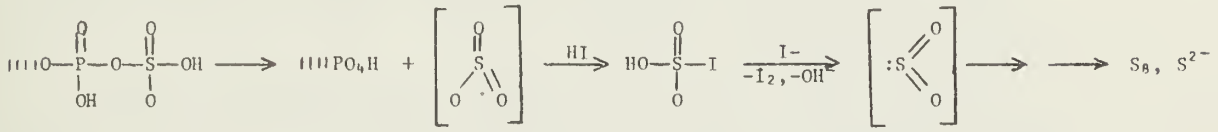
An interesting report has been published by Oae and Togo[13] on the biomimetic reduction of organic sulfonic acids and, more importantly, inorganic sulfate. The latter is the ultimate electron acceptor in the anaerobic respiration of certain bacteria, yet it is very resistant to known chemical methods of reduction. The authors observed that alkane and aryl sulfonic acids (RSO_3H) were cleanly reduced in a one-pot procedure with polyphosphoric acid (PPA), ethyl polyphosphate (PPE), or P_4O_{10} when in the presence of iodide ion. The mechanism is summarized in Scheme 1. The formation of the phosphosulfonate is the critical step, since this leads to the possibility of an S_N2

Scheme 1



type of displacement by iodide ion and the subsequent reductive eliminations. When R = OH (sulfuric acid), the same type of phosphosulfonate intermediate is formed, but it is degraded by a slightly modified mechanism (Scheme 2). A (1,2)-elimination

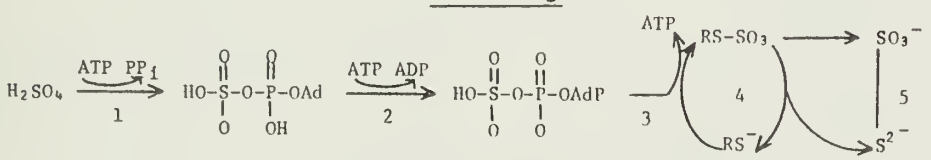
Scheme 2



leads to phosphoric acid and transient SO_3. The SO_3 can be further reduced to SO_2 and finally to elemental sulfur and sulfide.

The above mechanism closely resembles the enzymatic pathway for the reduction of sulfate[14], in which ATP is the phosphorylating agent (Scheme 3). The phosphosulfonate-adenine adduct is subject to nucleophilic displacement by an enzyme-bound sulfide, and the resulting thiosulfate either is directly reduced to disulfide, or is freed as sulfite ion which in turn is reduced to sulfide.

Scheme 3



1 = ATP-sulfurylase
2 = APS-kinase
3 = sulfotransferase
4 = thiosulfate reductase
5 = sulfite reductase

The field of biomimetic chemistry is full of potential. By copying the chemistry developed in biological systems, new synthetic procedures can be developed that are both milder and more selective. The most promising direction lies toward the rational design and synthesis of true organic catalysts that are inexpensive, stereospecific and enantioselective, and that can be applied toward the study of structure-function relationships as well as "ordinary" synthetic chemistry.

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THE APPLICATIONS OF LIQUID CRYSTALS AS HIGH RESOLUTION NMR SOLVENTS

Reported by Joseph C. Rongione January 31, 1985

Although most NMR studies have been done in homogeneous solvents, there are sometimes advantages in using as solvents a special class of liquids, partially ordered, called (misnamed) "liquid crystals".

The first use of a liquid crystal solvent in NMR studies was in 1963 by Saupe and Englert.[1] Since then, the use of Fourier transformations has greatly enhanced the versatility of NMR. These advances, most of which have employed isotropic solvents, have included an increased signal-to-noise ratio, more information from indirect spin-spin coupling (J coupling), the ability to observe low sensitivity nuclei and two-dimensional spectra.[2] Fourier transform has also been used to increase the efficiency of liquid crystal solvents. The advantages of using an anisotropic solvent include the measurement of chemical shift anisotropies, dipolar couplings between carbon, hydrogen and hetero atoms, conformational equilibrium activation parameters and relaxation times.[3-6]

Liquid Crystals

There are three basic classifications of liquid crystals; nematic, cholesteric and smectic. The nematic mesophase is the most random of the three, with the orientation of the long axis (shown by a unit vector called a director) changing constantly with position over large volumes of the mesophase. The random and rapid motion of molecules in the nematic mesophase makes it a good choice as a solvent for high resolution NMR.[7,8]

An optically active liquid crystal can form a special version of the nematic mesophase, the cholesteric mesophase. By virtue of the chiral center, the director in each layer rotates by some angle θ from the previous layer of molecules, so that there is a helical arrangement of the directors of consecutive layers of the liquid crystal. This mesophase is a poor choice for a high resolution NMR solvent due to this helical distortion.[7,8]

Figure 1

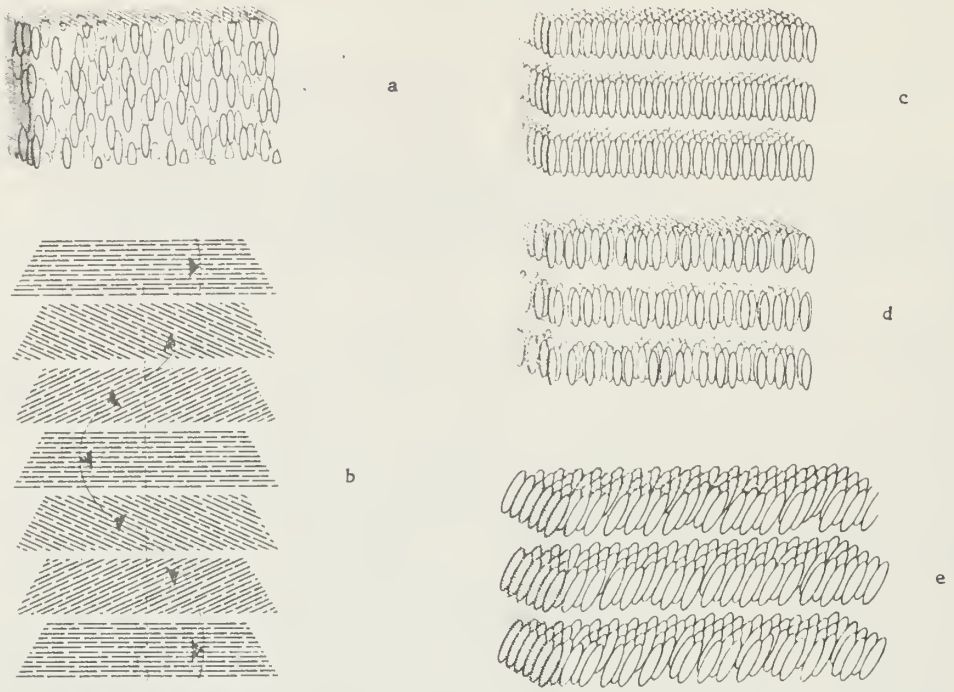


Fig. 1
idealized
representations of
a) nematic
b) cholesteric
c) smectic B
d) smectic A
e) smectic C
liquid crystals.[7]

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The most highly ordered mesophase is the smectic mesophase, of which there are eight subdivisions. There are layers of molecules in this mesophase, with the molecules lying parallel to each other. The subdivisions are classified by the degree of order in each layer and whether or not the molecules align themselves perpendicular to the plane of the layers of molecules.[7,8]

When placed in a magnetic field, liquid crystals have long-range order. This ordering results in a change in the free energy of the liquid crystal given by

$$\Delta G = -\Delta\chi \, B_0^2 \, (3\cos^2\alpha - 1)/6 \qquad \text{(Equation 1)}$$

where α is the angle between the magnetic field and the director and Δ, the anisotropy in the bulk diamagnetic susceptibility, equals $\chi_{||} - \chi_{\perp}$ ($\chi_{||}$ is the component along the director).[7] If the director is aligned parallel to the magnetic field it is said to have a positive diamagnetic anisotropy. If the director is perpendicular to the magnetic field, it has a negative diamagnetic anisotropy.[7]

Uses for Anisotropic NMR Solvents

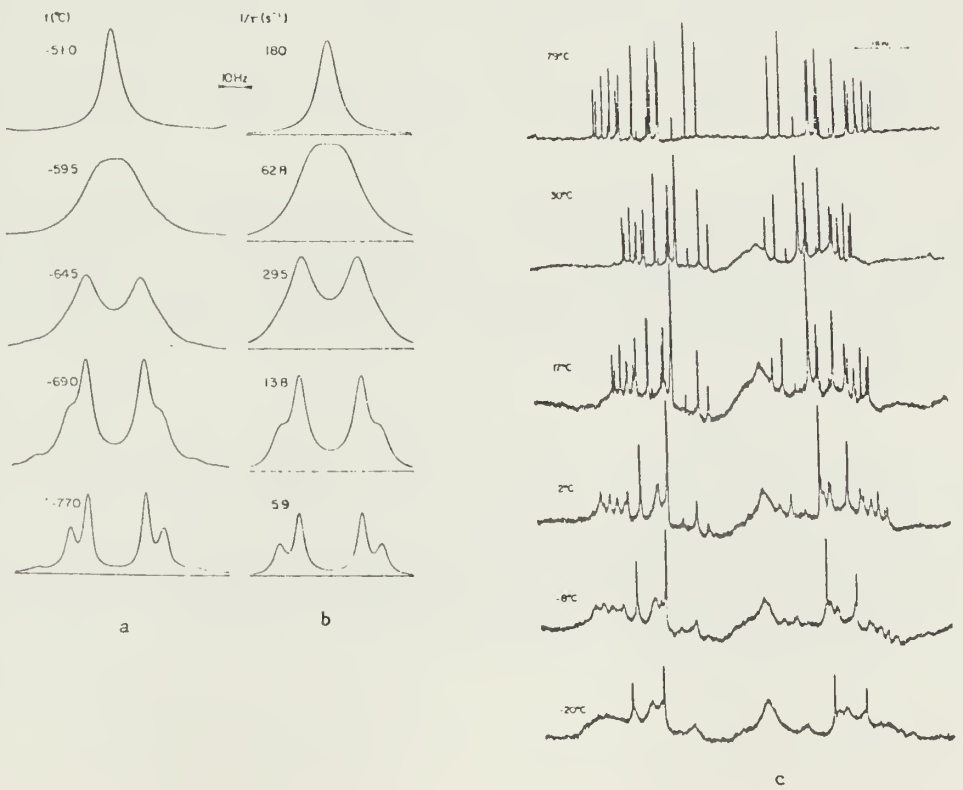
The major difference between isotropic and anisotropic solvents is that one sees intramolecular dipole couplings when anisotropic solvents are used. The rapid, non-random motion of solutes in liquid crystals allows intramolecular dipole interactions to be observed but the rapid movement causes the intermolecular dipole interactions to cancel out to zero.[7]

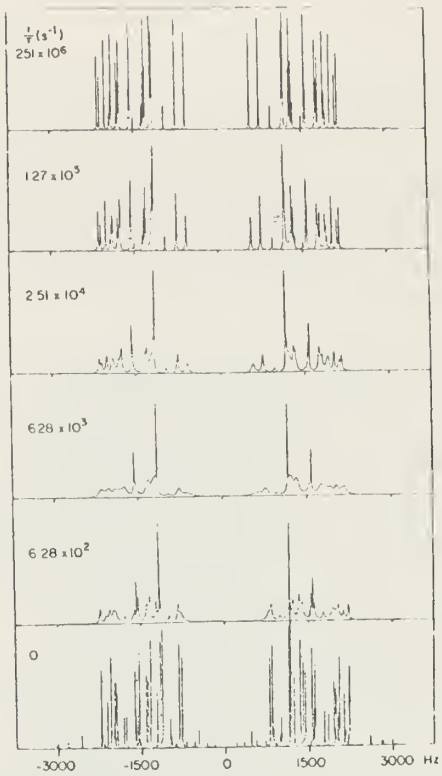
Along with dipole interactions, there are other factors that affect the form of the Hamiltonian operator of the nuclear spins of interest. There also is the Zeeman term (from the interaction of the magnetic field and the nuclear magnetic dipole moment), the indirect spin-spin coupling term (J coupling) and the nuclear quadrupolar interaction term, which comes into play for nuclei with $I > 1/2$.[10] This term shows up in ^2H NMR, where quadrupolar interactions are larger than dipolar interactions. This is advantageous in certain conformational equilibrium experiments, such as ring inversion of cyclohexane.[11]

The dipole interactions can greatly complicate proton spectra (Figure 2).[12] This increased detail contains the

Figure 2

Real (a) and simulated (b) spectra of S-trioxane in Freon and real (c) and simulated (d) spectra of S-trioxane in liquid crystal solvents





d

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interesting information not available using isotropic solvents. By matching the actual spectra to computer-generated spectra it is possible to derive the sought after parameters.[11,12]

The computer programs used are similar to the ones written for line shape analysis in isotropic solvents but are modified to include direct dipole interactions. LAOCOON II has been modified for use with liquid crystal solvents and other programs have been developed for quadrupolar interactions.[13,14]

After spectral analysis, it is possible to use the dipole coupling constants to calculate bond lengths and angles of the solute molecule. Due to the complex nature of the spectra of even simple molecules, this technique is somewhat limited in the size of molecule that can be analyzed.[6,10]

There are several equations that relate dipole couplings to bond lengths and angles, depending on the symmetry of the solute molecule.

For a molecule with a D_{2h} symmetry, like paradinitrobenzene, the equation looks like Equation 2.[15]

$$D_{ij} = -\gamma_i\gamma_j h[S_{zz}\langle(3\cos^2\theta_{ij}-1)r_{ij}^{-3}\rangle + (S_{xx}-S_{yy})\langle(\cos^2\theta_{ijx}-\cos^2\theta_{ijy})r_{ij}^{-3}\rangle \qquad \text{(Equation 2)}$$

where γ_i and γ_j are the gyromagnetic ratios of the nuclei, r_{ij} is the distance between nuclei i and j and θ_{ijx} is the angle between $\hat{r}_{ij}$ and the x principal axis $\hat{S}$. The <> brackets indicate vibrational averaging.[15] S_{zz} and $S_{xx}-S_{yy}$ are the principal elements of the Saupe ordering matrix, such that

$$S_{ab} = \langle 3\ell_a\ell_b-\delta_{ab}\rangle/2 \qquad a,b = x,y,z \qquad \text{(Equation 3)}$$

where ℓ_a and ℓ_b are the direction cosines of the director.[15,16]

Quadrupolar coupling constants can be calculated from ^{13}C-^{2}H direct couplings. Using data from spectra of $^{13}CDBr_3$ and $^{13}CDI_3$, it was possible to determine the quadrupolar couplings from Equation 4.

$$Qd = \frac{6.18\Delta}{\nu_{CD}\pm|J_{CD}|}\left\langle\frac{1/2(3\cos^2\alpha-1)}{r^3_{CD}}\right\rangle \qquad \text{(Equation 4)}$$

where r_{CD} is the distance between C and D (in Å), Δ is the separation of the quadrupolar doublet, ν_{CD} is the observed ^{13}C-D splitting, J_{CD} is the isotropic indirect coupling constant (last three in Hertz) and α is the angle between the instantaneous and equilibrium ^{13}C-D internuclear vector. The sign preceding J_{CD} was determined by a plot of Δ versus ν_{CD} graphed with points obtained at different temperatures.[17]

Finding chemical shift anisotropies ($\Delta\sigma$) is another useful feature of liquid crystal solvents. Using liquid crystals with opposite diamagnetic anisotropies appears to be the best way to do so. If it is possible to find a critical concentration and critical temperature, the coexistence of the two liquid crystals will result in the two spectra (one from the liquid crystal with positive $\Delta\chi$ and one from the liquid crystal with negative $\Delta\chi$) coexisting. The chemical shift anisotropy is

$$\Delta\sigma = \frac{\Delta\delta}{S_{||}} \qquad \text{(Equation 5)}$$

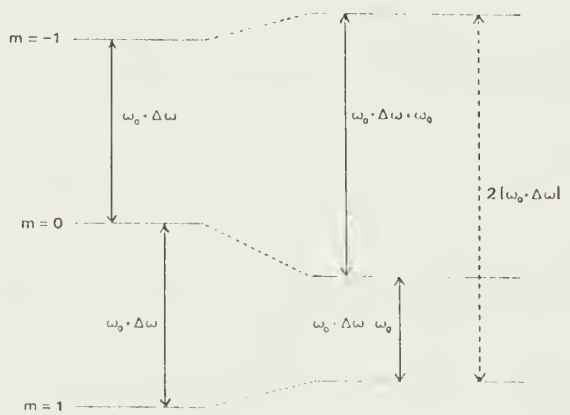
for a molecule with C_{3v} symmetry. The ordering parameter can be found from dipole coupling values and $\Delta\delta$ is the chemical shift difference between spectra in parallel and perpendicular alignments of the solvent.[18,19]

Another use for liquid crystal solvents is the separate determination of indirect spin-spin and direct dipole couplings (D_{ij}). This is best done by mixed ($+\Delta\chi$ and $-\Delta\chi$) liquid crystal solvents. Since both couplings are measured in the same solvent, (J coupling was usually measured in isotropic solvents and then used to calculate D_{ij} in anisotropic solvents) solvent effects are no longer a problem. This method allows easier measurement of heteronuclei-proton spin-spin coupling since double irradiation and 2D NMR techniques are not necessary.[20]

Two-dimensional (2D)NMR has been used to separate chemical shift and quadrupole splitting information for deuterated solutes. When a one-dimensional ^2H spectrum becomes too complex due to overlapping quadrupole doublets this technique would allow interpretation of the spectrum. There are presently two techniques available. The first, quadrupole echo spectroscopy, uses a pulse sequence similar to the spin echo sequence to refocus magnetization dephased due to quadrupole splitting. Acquisition starts at the point of refocusing of the magnetization. The second technique, multiple quantum spectroscopy, involves a double quantum transition (Figure 3).

Figure 3

Energy level diagram for I = 1 nucleus (double quantum transition is dashed arrows)



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($m = 1 \rightarrow m = -1$) which will be independent of quadrupole interactions. Of the two the multiple quantum spectroscopy has better chemical shift resolution.[21]

Deuterated solutes can be used to find activation parameters in liquid crystal solvents. Since the dipole interactions are assumed to be small, processes which affect the quadrupolar interactions can be

followed by ^{2}H NMR. Ring inversion of cyclohexane-d_{12} and p-dioxane-d_8 as well as the rearrangement of deuterated bullvalene have been studied using ^{2}H NMR.[11,12,22,23]

Carbon-13 NMR has been used in a similar manner. The rate of rotation around the C-N bond in 4-(dimethylamino)pyrimidine was followed by proton-decoupled ^{13}C NMR over a range of temperatures. The activation parameters were found by line shape analysis of the two methyl peaks.[24]

Limitations

As in every technique there are limitations to its application. Decoupling procedures for ^{13}C NMR are not as simple as those used for isotopic solvents. Many sequences have been developed and have been recently reviewed.[25]

Due to the dipolar interactions, only relatively small molecules can be observed with ^{1}H NMR. Even the perdeuterated solutes studied are not much more complex than the monosaccharide D-mannose.[21,23,24]

Another limitation is the temperature range available for a given liquid crystal. It is plausible that the liquid crystal may change from one mesophase to another over the temperature range of a particular experiment.[7,11]

Even with these limitations, NMR using liquid crystal solvents is a useful tool for activation parameter determination and molecular structure determination.

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ALIPHATIC NITRO COMPOUNDS: THEIR USE AS SYNTHONS OF EXCEPTIONAL VERSATILITY

Reported by Christopher J. Cramer February 4, 1985

Until quite recently, the use of the nitro functional group in aliphatic synthesis has been largely underappreciated. However, the great versatility of this group with respect to its activation of nearby carbons to act as either electron donors or acceptors (d^n and a^n synthons respectively, where the superscript indicates the number of the carbon atom n units away from the functionality in question) depending on experimental conditions has sparked widespread interest in the field.

Synthesis of Aliphatic Nitrocompounds

Many methods for the introduction of the nitro group have been reported in the literature of the last hundred years. These include the reactions of alkyl halides with silver nitrite and sodium nitrite under both homogeneous and phase-transfer conditions, the oxidation of amines, the oxidation of oximes, and the reaction of active methylene compounds with nitrate esters, nitric acid, or oxides of nitrogen[1]. In general, however, the above conditions are too harsh to be widely applicable. More recently, a number of milder methods has been developed, especially the oxidation of oximes[2a,b], nitrones[2c], and phosphine imines[2d]. Furthermore, many new synthetic strategies providing α-nitro- and α,α'-dinitrocycloalkanones have been reported[3], these compounds being useful both industrially[3a] and as precursors to nitroalkenes[4]. Nitroalkenes are further available via nitrodestannylation of vinyl stannanes[5], and oxidation of epoxyoximes providing a route into α-nitrocycloalkenones[6]. In addition, the nitromercuration of alkenes has been shown to provide an exceedingly mild and position-selective method for replacement of an olefinic proton by the nitro group[7]. Finally, the cobalt mediated synthesis of 1-nitroalk-3-en-5-ones has recently provided a route into functionalized homoallylic nitro compounds[8].

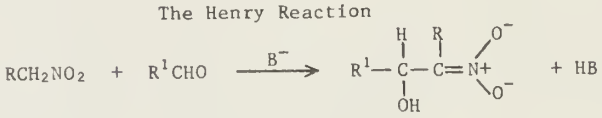
Reactions at the α-Carbon Atom of Nitroalkanes: Use as a d^1 Synthon

The relatively high acidity of α-nitro protons has been used to great effect for the last ninety years as evidenced by the vast amount of literature on the base catalyzed aldol-type condensation of nitroalkanes with aldehydes, the so-called Henry

reaction[1a,9] (Figure 1). Recent applications of this classical reaction have included the production of C-glycosides from 1-deoxy-1-nitroaldoses in yields of over 90%[10].

Figure 1

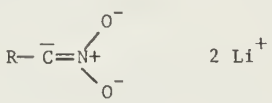
The Henry Reaction



Unfortunately, the use of electrophiles other than aldehydes in the Henry reaction leads predominantly to O-alkylation or acylation, and fails completely with ketones owing to the ready reversibility of the reaction and the stability of educts over products[11a]. Seebach and coworkers, however, have demonstrated that by the use of two equivalents of a strong base α,α-double deprotonation may be achieved, leading to a marked increase in C-nucleophilicity. This doubly deprotonated species may be represented as depicted in Figure 2. In a 5:1 THF:HMPA solvent

Figure 2

An α,α-doubly deprotonated nitronate

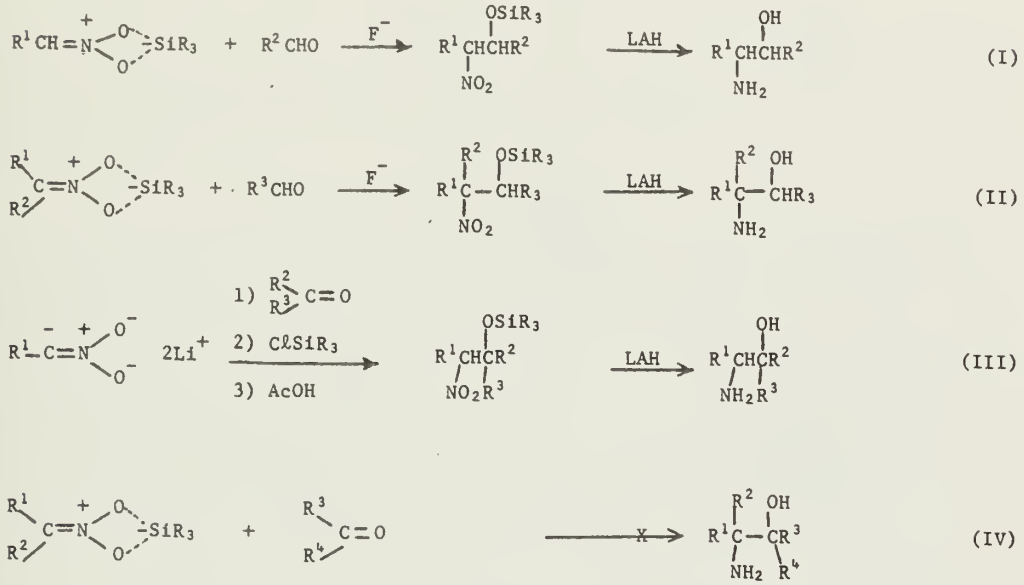


pair at -100°C these dianions may be alkylated, hydroxyalkylated, and acylated smoothly in moderate to good yields[1c,11]. Addition of copper iodide to the lithium dianion also allows smooth allylation at low temperatures[11e]. It has also been observed that these dianions add 1,2 to conjugated enones, in contrast with simple nitronates which add 1,4[1c]. The elaboration of these adducts has led to hitherto inaccessible α-amino acids, 2-aminoalcohols, α-hydroxyamino acid esters, α-hydroxyimino esters, α-hydroxyimino ketones, α-diketones, and α-ketoesters[11f].

Another improvement developed by Seebach, et al. involves the use of silyl nitronates, derived from O-silylation of the corresponding primary and secondary nitronates. These silyl nitronates undergo fluoride catalyzed addition to aldehydes

smoothly and in high yields to produce 2-nitroalcohol O-silyl ethers[12]. Lithium aluminum hydride reduction of these ethers yields 2-aminoalcohols in excellent yields, in contrast to 2-nitroalcohols which undergo retroaldolization under the same conditions. The synthetic importance of these vicinal amino alcohols can be seen in the Tiffeneau-Demjanov and related deaminative semipinacol rearrangements[13]. Thus, as shown in Scheme I, 2-amino alcohols of types I, II, and III are available with only type IV being unobtainable by this method.

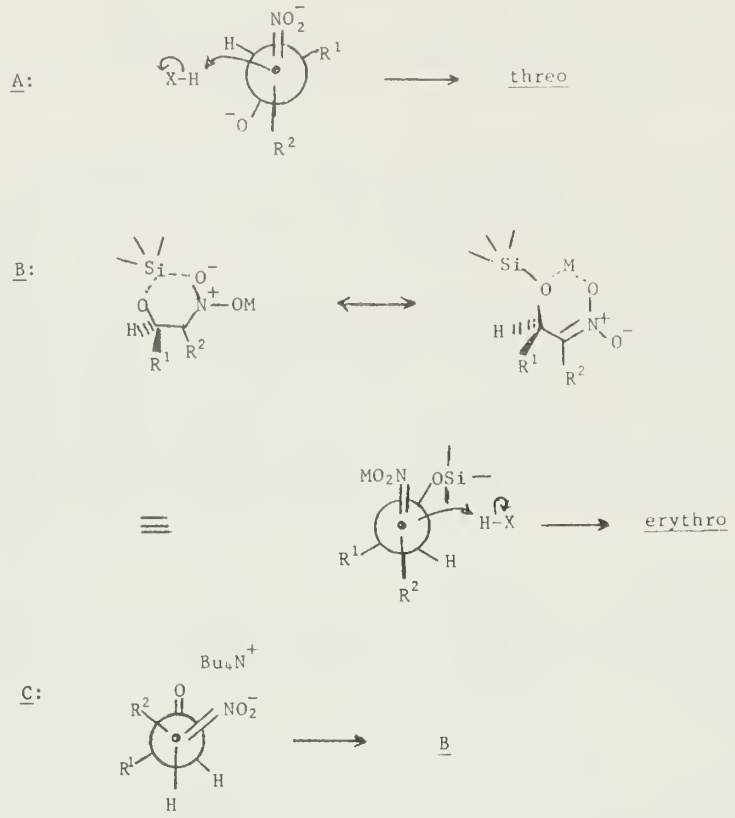
Scheme I



However, the greatest advantage of either of the above two modifications of the Henry reaction, which always gives a thermodynamic mixture of diastereomers, is their ability to provide diastereoselective aldolization or protonation leading to highly enriched threo or erythro products[14]! threo-Enriched nitroaldols are produced by low temperature diastereoselective protonation of doubly deprotonated nitroaldols. The degree of selectivity is strongly dependent upon the presence of hexamethyl phosphoramide (HMPA). Essentially pure erythro products are obtained from either the low temperature protonation of O-silylated nitroaldol nitronates or fluoride

catalyzed O-silylnitroaldol condensations. The transition states proposed to account for these observations are illustrated in Scheme II. In A, charge repulsion of the two negative charges coupled with protonation from the less hindered

Scheme II



face of the nitronate leads to threo product. In B, chelation by lithium and/or silicon, again followed by sterically directed protonation leads to erythro product. Finally, in C, the aldol reaction follows a general topological rule for joining two two-dimensionally chiral stereocenters[20b]. Reduction of these nitroalcohols proceeds with either lithium aluminum hydride or Raney nickel with no loss of stereochemical integrity.

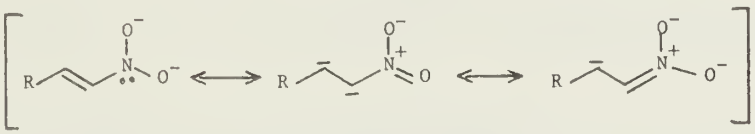
Reactions at the β-Carbon Atom of Nitroalkanes: Use as a d^2 Synthon

The normal reactivity of the β-carbon in nitroaliphatic compounds is a^2 (vide infra). However, when suitable

functionality is present on the β-carbon (e.g. phenyl, carboalkoxy, or vinyl), or if there is only one α-nitro proton, deprotonation of the nitroaliphatic under analogous conditions for α,α-deprotonation leads to α,β-double deprotonation[1c,11b,15]. These compounds, depicted in Figure 3, have been referred to as "super-enamines" since this umpolung of a nitroaliphatic's normal umpolung (that is, "double-umpolung")

Figure 3

An α,β-doubly deprotonated nitronate



returns the reactivity of the β-carbon to that normally found in enolates or enamines, but with a great increase in nucleophilicity.

Thus, 2-nitropropane can be alkylated, hydroxyalkylated, or acylated in moderate yields at low temperature[11b]. Double deprotonation of 2-arylnitroethanes produces solutions of dianions which are stable for many hours at room temperature, even with halo- and alkoxy-substituted aryl substituents[1c]! These nucleophiles combine in good to excellent yields with alkyl halides, aldehydes, and ketones, and undergo conjugate additions to both enones and nitroolefins. Many of these reactions may be performed titrimetrically, the dianion being a deep red in solution. Finally, the acidifying nature of the ester in β-nitropropionates allows β,β-dialkylation by regeneration of the doubly deprotonated species following the initial alkylation.

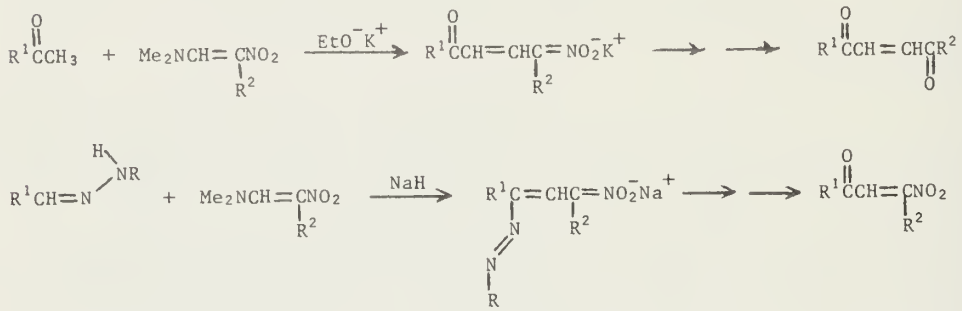
Reactions at the β-Carbon Atom of Nitroalkenes: Use as an a^2 Synthon

The addition of active methylene compounds to nitroolefins is one of the most efficient C-C bond forming reactions involving nitrocompounds[1a]. This reaction is most successful with well-stabilized anions, yields decreasing with increasing reactivity of the nucleophile, although alkyl groups can be added as dialkyl cuprates or cadmium alkyls[16]. Furthermore, even highly reactive anions such as n-butyl lithium may be

added with reasonable success by use of extremely low temperatures (-120°C)[1c]. Thus, sulfur-stabilized anions [16a], oxoalkane polyanions[16b], lithium enolates[16d-f], and vinyl Grignard reagents[7] have all been successfully used as donors in Michael additions to nitroolefins.

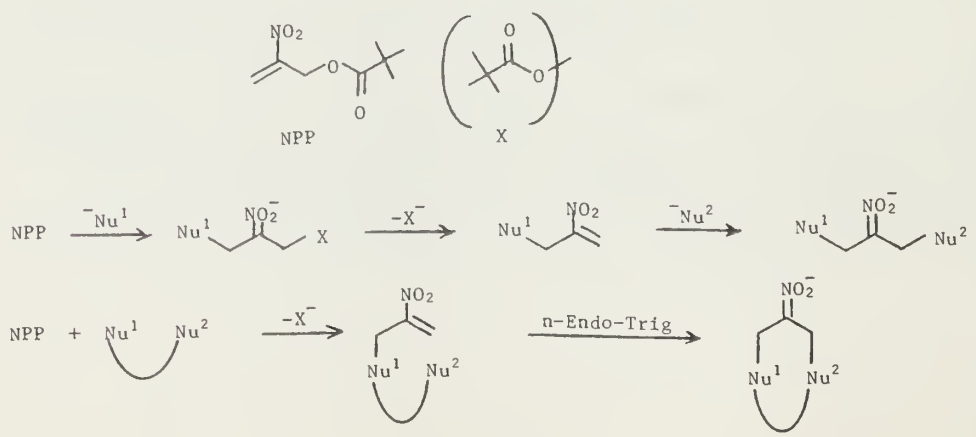
The use of β-nitroenamines as Michael acceptors and the further conversion of the Michael adducts to α,β-unsaturated 1,4-dicarbonyl compounds have been investigated by Severin and co-workers[17]. The use of aldehyde hydrazone anions in Michael additions to β-nitroenamines to give β-nitroenones (vide infra) has also been investigated[18] (Scheme III).

Scheme III



As an interesting extension of this a^2 reactivity, Seebach and co-workers have developed an $a^2,a^{2'}$ multiple coupling reagent[19]. 2-Nitro-3-pivaloyloxy-1-propene (NPP) serves as a nitroallylating reagent for the first added equivalent of nucleophile[19a,b], and addition of a second nucleophile then effects a convergent coupling through a 3-carbon spacer which may be converted into various functionalities at the 2-position (vide infra)[19c] (Scheme IV).

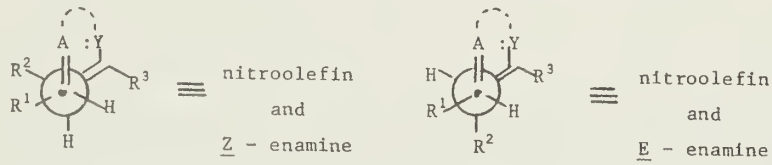
Scheme IV



Once again, however, the real utility of these Michael additions is demonstrated by recent advances which have demonstrated that they may be induced to proceed with high degrees of enantio- and diastereoselectivity[20]. The reaction of open-chain enamines with open-chain nitroolefins has been shown to lead to γ-nitroketones with diastereomeric purities exceeding 90%. In solvents affording poor charge solvation, the transition states shown in Figure 4 have been shown to be quite generalizable, and apply as well in this instance[20b].

Figure 4

Transition states for syn approach of two two-dimensionally chiral centers

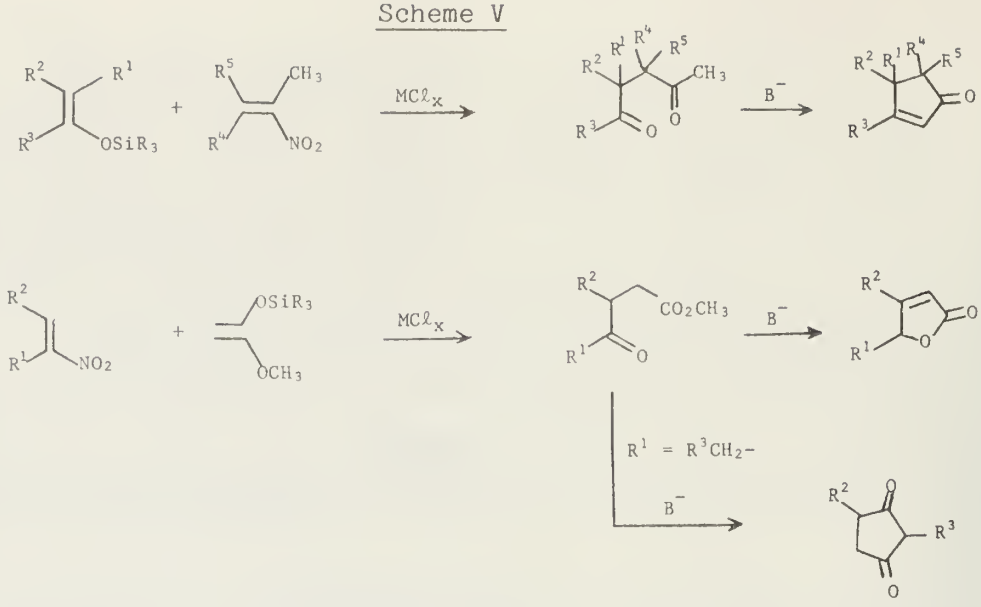


ul approach (Re^*Si^*) lk approach (Re^*Re^*)

Furthermore, when chiral enamines derived from prolinol are used, enantiomeric excesses exceeding 90% have been observed in the products of the Michael addition[20c]. The relative topicity of the reactants' approach in these reactions is invariably lk,ul-1,4.

Another approach to improving the versatility of nitroolefins as Michael acceptors has been the use of Lewis acids to catalyze the addition. Yoshikoshi and co-workers have investigated the reactions of silyl enol ethers and silyl ketene acetals with nitroolefins under Lewis acid catalysis to generate 1,4-diketones and γ-ketoesters (the initial adducts undergoing an in situ Nef reaction to generate the carbonyl)[21]. These species may then be further elaborated making this a convenient, regiospecific route to cyclopentenones, α,β-unsaturated γ-butyrolactones, and cyclopentane-1,3-diones (Scheme V).

Scheme V



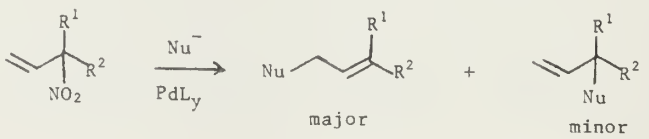
Another variation upon this theme investigated by Yoshikoshi and co-workers has involved the fluoride catalyzed Michael additions of 1,3-diketones to nitroolefins, providing a convenient route into 3-acylfurans and 2-substituted 1,3-dicarbonyl compounds[22]. Interestingly enough, the ring closure step in the acylfuran synthesis involves the formal S_N2 displacement of NO_2^- by an oxyanion[22b,c], thus conferring an a^1 reactivity to carbon 1 of the nitroaliphatic intermediate. We have thus come full circle in the reactivity of carbons 1 and 2 in nitroaliphatics.

Miscellaneous Chemistry of Nitroaliphatics at More Remote Positions

The chemistry of nitroaliphatics at more removed positions is much less rich than that at C-2 and C-1, but it is still well worth noting. Palladium(0) catalyzed alkylation and amination of allylnitroalkanes provides not only another example of a^1 reactivity, but more interestingly, an example of a^3 reactivity[23] (Figure 5).

Figure 5

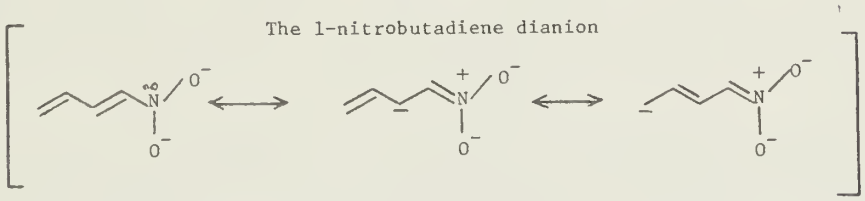
Palladium catalyzed a^1 and a^3 additions to nitroaliphatics



At Carbon-4, examples of both a^4 and d^4 reactivity exist. Double deprotonation of 4-nitro-1-butene generates the 1-nitrobutadiene dianion, which is depicted in Figure 6. This

Figure 6

The 1-nitrobutadiene dianion



anion can be alkylated and hydroxyalkylated with good selectivity for the δ-position. It further acts as a Michael donor with 100% δ-selectivity, thus making this dianion formally a d^3 γ-enolate of crotonaldehyde[1c,11c].

As an example of a^4 reactivity. Severin and co-workers have extended their research on nitroenamines to show that active methylene compounds will add regioselectively to the 1-position of 1-dimethylamino-4-nitrobutadiene to afford products analogous to those described above in Scheme III but now extended by an unsaturated 2-carbon unit, thus affording α,β,γ,δ-doubly unsaturated 1,6-diketones[24].

As a final example of the umpolung of reactivity provided by nitroaliphatics, it has been shown that the use of β-nitroenones as the 2π component in [4+2] cycloadditions in addition to substantially decreasing the temperatures required for cycloaddition leads to exactly the opposite regioselectivity predicted for the simple enone[6]!

Removal/Elaboration of the Nitro Group From Nitroaliphatics

In addition to those methods already discussed above there are a number of other possible transformations of the nitro group. The literature concerned with the conversion of the nitro functionality to ketone or carboxylate (the Nef reaction) is vast[1a,c,25]. Not surprisingly, given the often capricious nature of the reaction, a large number of variants has recently been reported including reductive methods such as Ti(III) or V(II)[21a,b,25a], oxidative methods such as $S_2O_8^{2-}$ or ascorbate[25b], and neutral methods such as silica gel[17b]. Methylation of the aci-nitronate, the formal removal of

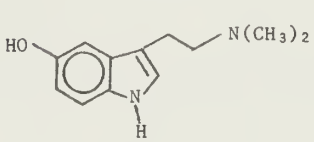
formaldehyde to the oxime, and trans-oximation has also been shown to be effective[17a]. Reduction with zinc or iron to the hydroxylamine with subsequent intramolecular formation of a nitrone which is then used in a [3+2] cycloaddition is a particularly elegant method which has also been investigated[7]. Reductive methods to the amine have already been discussed (vide supra)[12a,14b]. Oxidative dimerization is also possible with Ag(I)[25d]. A number of methods also exist to effect 1,2-elimination of the nitro group[1a]. Finally, a variety of one-electron reductive methods exist for the substitution of a hydrogen for the nitro group[1c,10b,25e,f].

Application of Nitroaliphatic Chemistry to Natural Product Synthesis

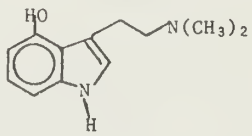
In addition to the industrial production of d,l-lysine and ε-caprolactam[3a], nitroaliphatic chemistry has played a major role in several recent total syntheses including the psychomimetic hallucinogens bufotenine and psilocene[26], the furanoterpenoids ligularone and isoligularone[27], and the furanoelemanoids curzerenone and epicurzerenone[28] (Figure 7).

Figure 7

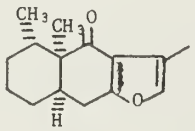
Some natural products synthesized using nitroaliphatics



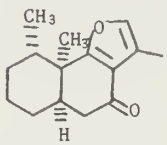
bufotenine



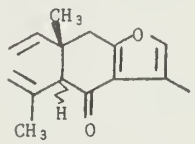
psilocene



ligularone



isoligularone



curzerenone (H_α)
epicurzerenone (H_β)

Given their impressive scope as electron donors and acceptors at so many positions, it is clear that nitroaliphatic compounds will find increasing use in future synthetic endeavors.

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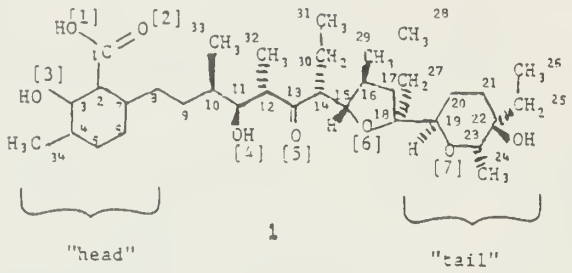
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CONFORMATIONAL STUDIES ON LASALOCID A, AN IONOPHORIC ANTIBIOTIC

Reported by Greg M. Anstead February 11, 1985

Ionophores are low molecular weight compounds of synthetic or microbial origin that are able to form lipid soluble complexes with cations.[1,2,3,4] The carboxylic polyether family of ionophoric antibiotics consists of open-chain molecules containing polar functionalities, one of which is a terminal carboxyl group.[5] All are capable of forming cyclic structures by head-to-tail hydrogen bonding.[2] The polyether lasalocid A (X-537A) (**1**)[6] is unique among ionophores in its ability to bind a myriad of cations: alkaline and rare earths, alkali, transition, and post-transition metals, and 1° and 2° ammonium ions.[2]



1

The structure of lasalocid A (las) was originally deduced from X-ray crystallographic analysis of its Ba salt.[7] Since that time, crystallographic investigations have been performed on numerous forms of las, including the free acid, its 6-bromo derivative, the Ag salt, its 6-NO_2 derivative, the Na and Cs salts, and one ammonium salt, some of which are solvated.[8,9] Las adopts essentially the same conformation in all these crystals. There is head-to-tail hydrogen bonding between the carboxyl group and O_8-H, O_4-H, and O_3-H. In general, the las units exist as head-to-tail dimers in the solid state.[8]

The behavior of las in solution has been probed by a diverse array of physical methods. Potentiometry,[10] the fluorescence of the salicylate group,[5,11,12] and circular dichroism[5,12,13,14,15,16] have provided the stoichiometries and formation constants of many complexes. From the changes in

optical activity observed in solvents of varying polarity, three solution conformations of las and its complexes have been proposed: an open chain form, a cyclic conformer with three hydrogen bonds, and a partial ring structure.[5,17] Perturbations of the CD spectra also suggest the mode of attachment of the ionophore to the cation.[13,15,16]

Optical spectroscopy of complexed lanthanide ions has also indicated stoichiometry, conformation, and mode of attachment.[18,19] These methods have included observations of the circularly polarized and salicylate-sensitized luminescence of Tb^{3+}.[19]

Magnetic resonance techniques have provided the most detailed data on the solution geometry of las and its complexes. Extensive proton decoupling experiments performed on las and its Na complex in nonpolar solvents indicate a backbone conformation similar to the crystalline Ba salt.[20] Rotational correlation times, obtainable from T_1 values, have afforded information on the monomeric or dimeric status of several las species.[21,22,23] Cation-oxygen distances for various complexes have been calculated from measurements of the paramagnetic enhancement of the ^{13}C relaxation rates.[24,25,26] Information on the mode of complexation and conformation has also been provided by analysis of ^{1}H and ^{13}C chemical shifts.[27,28] Variable temperature ^{1}H NMR studies suggest a dynamic, intramolecular oxygen exchange for las complexes in nonpolar media.[28]

The study of the conformation of lasalocid is illustrative not only of the complexity of molecular topology but also of the powerful methodology available for unraveling this complexity.

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THE CHEMISTRY OF α-SULFINYL CARBANIONS

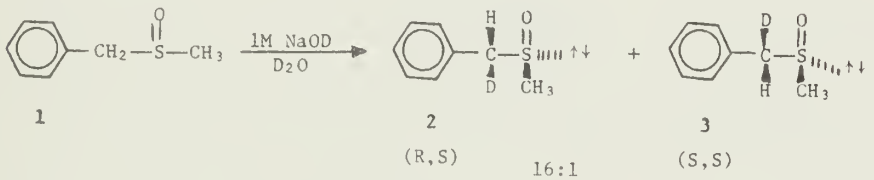
Reported by John E. Marlin February 14, 1985

α-Sulfinyl carbanions have received much attention since the mid-1960's. Initially, interest was focused on the mechanism of diastereoselectivity found when treating these carbanions with a variety of electrophiles. Carbanions derived from chiral sulfoxides have been the subject of ab initio calculations and ^{1}H and ^{13}C NMR spectroscopic studies. Recently, these functional groups have been incorporated in the formation of key intermediates for the stereoselective syntheses of natural products.[1,2]

Stereochemistry

In 1965, Rauk, Buncel, Moir, and Wolfe[3] discovered that the diastereotopic methylene protons alpha to a sulfoxide could be exchanged with deuterium in a highly stereoselective manner.

Scheme I

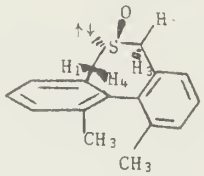


It was suggested that the methylene protons assumed a preferred conformation with respect to the chiral sulfoxide group and, in the case of the S-sulfoxide, the pro R proton was more acidic.[4] There followed many attempts to determine the structure of the incipient carbanion and to explain its stereoselectivity. Durst[4b] studied the stereochemical aspects of the deuteration of **1** by two methods. First, the relative rates of exchange of the diastereotopic methylene protons as a function of solvent polarity using Na+ counterions in deuterated protic solvents were compared. The results show that the relative rates of exchange (the pro-R vs pro-S proton) ranged from 14:1 (D_2O/NaOD) to 1:2 (t-butanol-OD/Na-t-butoxide). The second set of experiments compared the diastereomeric ratios obtained by the rapid D_2O quench of the α-lithiosulfoxide of **1**

in aprotic solvents. The same trend was observed as solvent polarity changed. Furthermore, upon lowering the temperature in THF, the stereoselectivity increased from 1:7.5 to 1:15.

To evaluate the synthetic utility of these compounds, α-lithiosulfoxides were alkylated and hydroxyalkylated.[5] Alkylation with methyl iodide proceeded in high yield and with diastereomeric ratios identical to those obtained in the D_2O quench. However, the absolute configuration at carbon of the resulting α-phenethylmethyl sulfoxide was opposite to that of the α-deuteriobenzylmethyl sulfoxide. Hydroxyalkylation with various ketones and aldehydes produced diastereomeric ratios and absolute configurations identical to those from deuteration. It was concluded from these experiments that deuteration and hydroxalkylation occur with retention of configuration and alkylation occurs with inversion of configuration.

Studies undertaken with conformationally fixed sulfoxides have proved interesting as well. Fraser, Schuber, Wigfield, and Ng studied the kinetic exchange of diastereotopic protons with deuterium in sulfoxide **4**.



4

In $CD_3OD(NaOD)$, the relative exchange rates were $H_1 = 1$, $H_2 = 200$, $H_3 = 7500$, and $H_4 = 30$. Assuming that the exchange rates are directly related to carbanion stability, the most stable carbanion is that formed trans to the sulfur-oxygen bond.

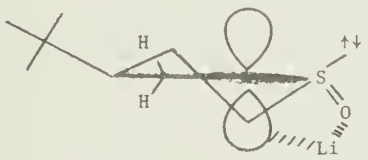
This result was corroborated by Hutchinson[7] and coworkers who studied deuterium exchange of cis and trans-4-phenylthiopyran-S-oxide. They concluded that the order of carbanion stabilities is a) trans to the sulfoxide oxygen, b) gauche to the sulfoxide oxygen and gauche to the sulfoxide lone pair, and c) trans to the lone pair.

Structure

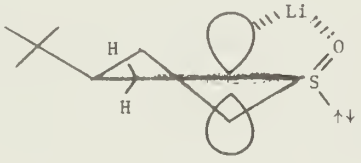
Discrepancies still exist between theoretical calculations and NMR studies concerning the actual structure of an α-sulfinyl carbanion. Is it planar like an enolate anion or pyramidal like

an α-sulfenyl carbanion? Comprehensive ^{1}H and ^{13}C studies of α-lithio-4-t-butylthiacyclohexane-1-oxides (**5** and **6**) suggest the α-metallated carbanion is planar[8] but conflict with theoretical calculations performed by Wolfe, Rauk, and Csizmadia.[9] These calculations led to the conclusion that the most stable configuration of an α-sulfinyl carbanion is pyramidal with the electron pair of carbon gauche to the sulfur-oxygen bond and the sulfur lone pair.

$^{3}J_{HH}$ coupling constants are not in agreement with simple boat and chair conformations. Two twist conformations and two half chair conformations are also unlikely due to incompatible proton-proton coupling constants. The coupling patterns are, however, compatible with the structures **5** and **6**.



5



6

The ^{13}C study was undertaken to gather more evidence about the hybridization of the metallated carbon. In particular, the $^{1}J_{CH}$ values of the α-lithio derivatives were determined. The two most important factors governing the direction and magnitude of a change in $^{1}J_{CH}$ are a change in hybridization[10] ($^{1}J_{CH}$ increases as $sp^3 \rightarrow sp^2$) and the spin density in the s orbitals of both nuclei[11] ($^{1}J_{CH}$ decreases as charge increases). The data are given in Table 1.

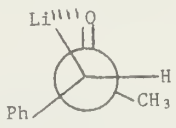
Arylmethyllithio derivatives[10,12] and phosphorous ylides[13] have also been studied by ^{13}C NMR. The hybridization at carbon determined for these compounds is in agreement with X-ray studies.[14] Thus, for metallated carbon atoms, the $^{1}J_{CH}$ coupling constant is a reliable alternative for qualitative information on hybridization.

The data show a positive $\Delta^{1}J_{CH}$. Since a decrease in the $^{1}J_{CH}$ coupling constant for a given hybridization state reflects an increase in negative charge on the carbon atom, the significantly larger values of $^{1}J_{CH}$ are a result of rehybridization.

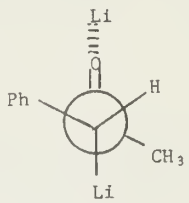
Table 1

	Solvent	T(°C)	$^{1}J_{^{13}C-H}$	ΔJ	Δδ
$C_6H_5-\overset{O}{\overset{\|\|}{S}}-CH_2^-$	THF	30°C	155.5	+16.5	-11.9
	THF/HMPA		155.5	+16.5	- 7.25
	THF	30°C	157	+18	- 9
	THF/2.2.2	-60°C	146	+ 7	- 2.4
5	THF	30°C	157	+19	-13
6	THF	30°C	158	+19	- 3

While early ab initio calculations[9] of α-sulfinyl carbanions suggested structures contrary to those found experimentally, recent calculations[15] are in accord with experimental data[16] that suggest that the stereochemistry of α-lithiosulfoxides is affected by chelation as well. These calculations determined that the most stable conformation of α-lithiobenzylmethyl sulfoxide is structure **7**.



7



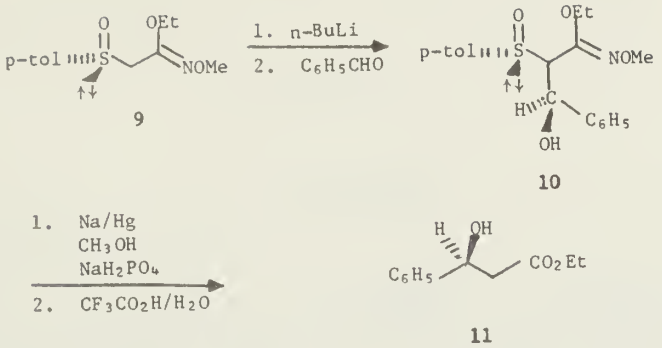
8

However, in the presence of excess Li^+, an intermolecular Li-O bond is preferred and the Li-C bond is antiperiplanar to oxygen[15b] (**8**). Experimentally, Durst found that the ratios of diastereomers from the methylation of α-lithiobenzylmethyl sulfoxide changed from 15:1 with one equivalent of methyllithium to 0.45:1 with one equivalent of methyllithium and sixty equivalents of lithium bromide.[16a]

Applications

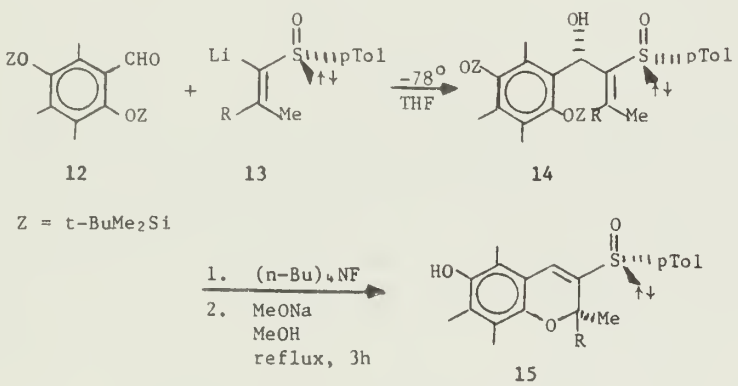
Asymmetric reactions involving chiral sulfoxides and their α-lithio carbanions are receiving increased attention in the literature. The use of (R)-(p-tolylsulfinyl)-ethyl N-methoxy acetimidate **9** as an effective chiral acetate equivalent in asymmetric condensations with aldehydes (Scheme II) has recently been reported.[17]

Scheme II



The choice of the ethyl N-methoxyimidate function was dictated by the possible direct conversion of this group to esters by acid hydrolysis or aldehydes by reductive treatment. In addition, reductive desulfurization accompanied by conversion of the N-methoxyimidate group to the ester could be accomplished in one pot with Raney nickel. Solladie and Moine[18] performed an enantiospecific synthesis of the chroman ring of α-tocopherol (Vitamin E) using chiral vinyl sulfoxides as shown in Scheme III.

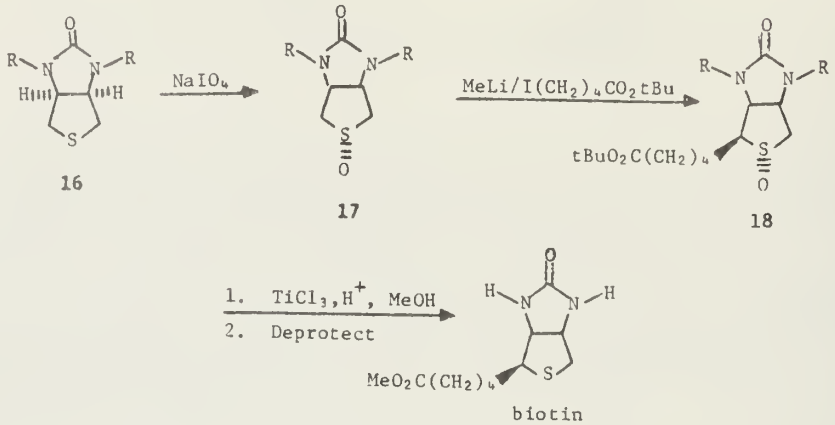
Scheme III



Although this lithio reagent is a vinyl carbanion, two aspects of this reaction are worth noting: 1) the addition of the lithio reagent **12** to the aldehyde **13** generates only one diastereomer and 2) ring closure leads to stereospecific formation of **15** in 96% yield.

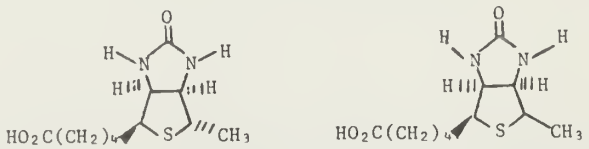
A total synthesis of biotin based on the stereoselective alkylation of chiral sulfoxides has also been achieved.[19] Starting with the intermediate sulfide **16** prepared from known chemistry, oxidation with $NaIO_4$ afforded the sulfoxide **17** (Scheme IV).

Scheme IV



16 **17** **18** biotin

The alkylation is completely stereoselective with the side chain introduced trans to the sulfur-oxygen bond in 80% yield. This synthesis is also very well adapted to the preparation of biotin analogues since in the key step, the sulfoxide **17** can be treated with a variety of alkylating agents. Substituents may also be introduced at the α'position, owing to the high regioselectivity of the alkylation of sulfoxides. In addition, the configuration at sulfur can be easily inverted by Meerwein's salt.[20] Thus, a great number of analogues can be synthesized (e.g. isomeric 5-methylbiotins **19** and **20**).

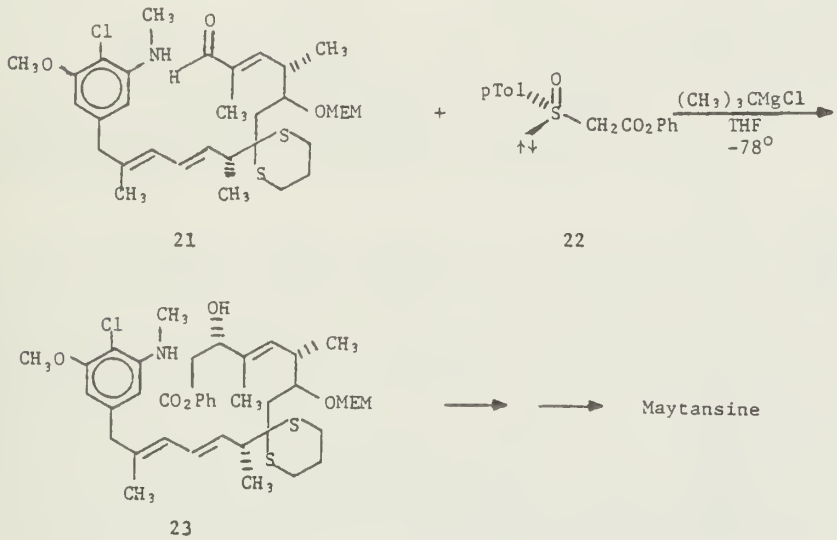


19 **20**

α-Sulfinyl carbanions have also been employed in a synthesis of maytansine[21] (Scheme V). This method produces a diastereomeric ratio of 93-7 in contrast to the addition of

α-lithioacetic acid tetrahydropyranyl (THP) ester to **21** which furnished a 1:1 mixture of the THP ester corresponding to **23** and the 3-(R)-epimer.

Scheme V



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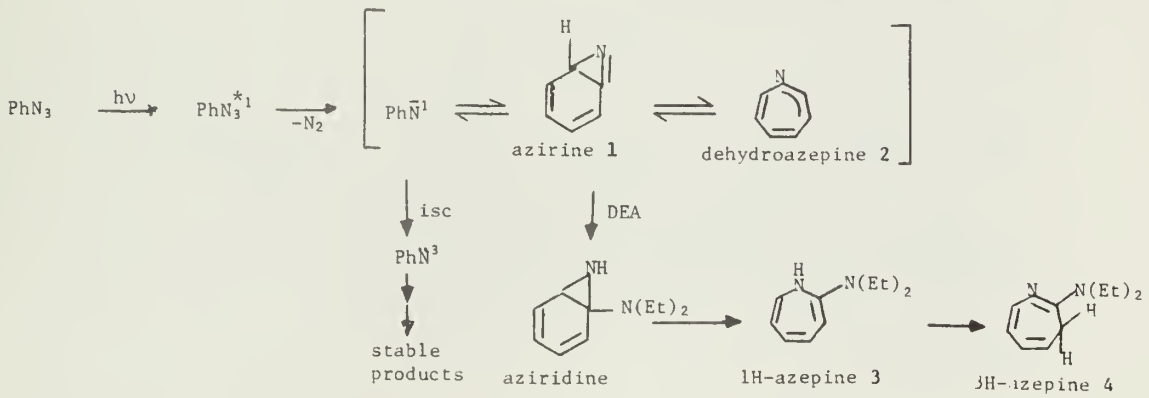
MECHANISMS OF PHOTODECOMPOSITION OF PHENYL AZIDE AND p-NITROPHENYL AZIDE

Reported by Tsuei-Yun Liang February 18, 1985

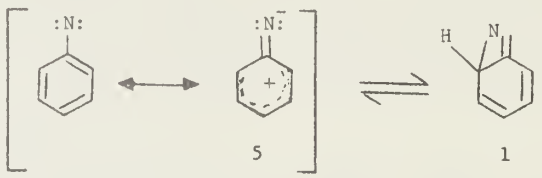
The photochemistry of aromatic azides has been studied for quite some time.[1] This topic has gained considerable attention because these compounds are useful in photoimaging systems and as photoaffinity labels.[2] In both of these applications loss of molecular nitrogen to generate an extremely reactive intermediate is thought to play a critical role.

Irradiation of phenyl azide in an inert solvent gives mostly insoluble tar and a small amount of azobenzene.[3] Triplet sensitization studies[4] show that azobenzene comes from the triplet phenyl nitrene. The yield of azobenzene depends on the concentration of the phenyl azide and on the power of the light source.[5] Irradiation of phenyl azide in the presence of a nucleophile, diethylamine, leads to 2-diethylamino-3H-azepine **4**. The azepine **4** is believed to arise from singlet phenyl nitrene in equilibrium with azirine **1**[6] and dehydroazepine **2**[7], initially giving 1H-azepine **3**, which rearranges to 3H-azepine **4**. The dehydroazepine **2** is the predominant species in the matrix at 8°K.[7b] That is the first-formed transient product detected in the pulsed irradiation of phenyl azide.[5] Formation of the 1H-azepine **3** is a two-step process from the singlet transient to azirine **1**. The second step is independent of amine concentration. These results are summarized in Scheme I.

Scheme I



Two factors have been suggested to be responsible for the lack of reactivity of phenyl nitrene in intermolecular insertion reactions with saturated hydrocarbons and addition to olefin. The nitrene may be in equilibrium with a closed shell azirine **1**.[8] It may also have large resonance contribution from the dipole form **5**, which would diminish the electron deficiency at nitrogen.[9] It should be possible to increase the electrophilic



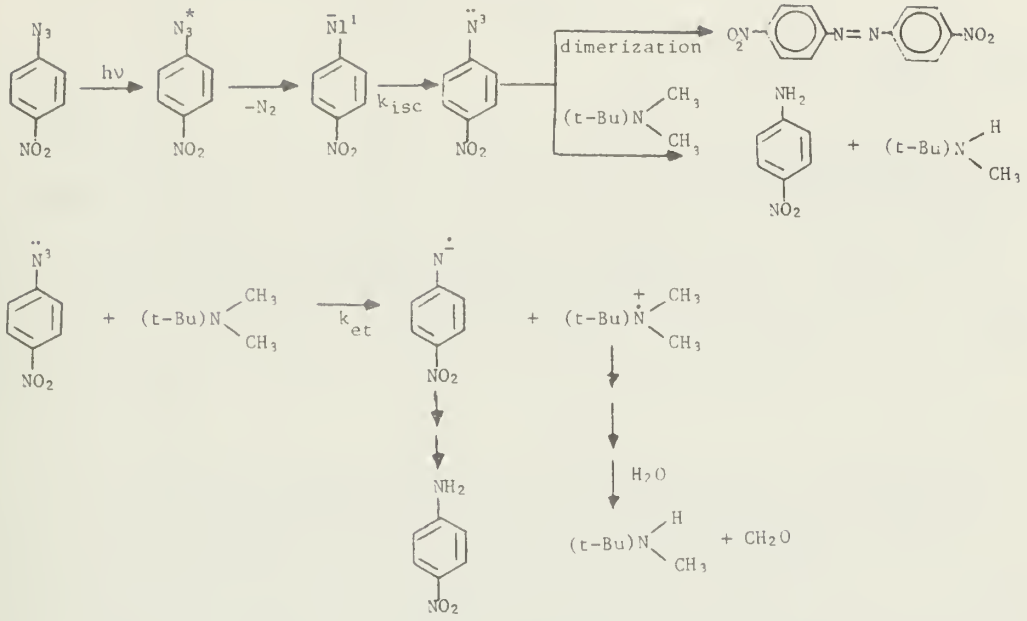
5 1

character by introducing electron-withdrawing substituents, such as nitro group.

The photolysis of p-nitrophenylazide gives neither intermolecular substitution nor is azepine formed in the presence of diethylamine. Photolysis products in the presence of amine are 4,4'-dinitroazobenzene and p-nitroaniline. The transient absorption from irradiation of p-nitrophenylazide is assigned to the triplet p-nitrophenyl nitrene on the basis of the low temperature EPR spectrum,[10] low temperature UV-Vis absorption spectrum[11] and nanosecond laser spectroscopy.[12]

The triplet nitrene dimerizes to 4,4'-dinitroazobenzene by a second order process with a rate constant of $1 \times 10^{9} M^{-1} S^{-1}$, ten times less than the diffusion controlled rates. Triplet p-nitrophenyl nitrene generated in the presence of a nucleophile (t-butyldimethylamine) gives p-nitroaniline and t-butylmethylamine. These products are quite different from those of singlet phenyl nitrene. This is supported by measuring the power dependence of the yield of 4,4-dinitroazobenzene. The triplet p-nitrophenyl nitrene reacts with t-butyldimethylamine by a single-electron transfer to form p-nitrophenyl nitrene radical anion, as shown in Scheme II. This is supported by analysis of product isotope effects.

Scheme II



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THE HALOFLUORINATION REACTIONS: SCOPE AND APPLICATIONS IN RADIOFLUORINATION

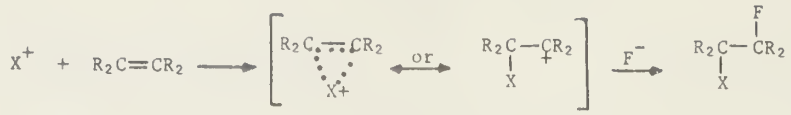
Reported by Dae Yoon Chi February 21, 1985

Radiopharmaceuticals have been widely used to characterize the distribution and concentration of receptors for hormones and drugs and to study how these change in relation to a variety of diseases. To accomplish these purposes, the radiopharmaceuticals must be carefully designed to optimize both their binding selectivities and their nuclide emission properties.

Of the various positron-emitting radionuclides available for preparing radiopharmaceuticals, fluorine-18 would appear to be an ideal label from the radiochemical point of view:[1] Fluorine-18 has a half life (110 min) adequate to permit rather complex syntheses but short enough to minimize radiation dose; it also has a relatively low particle energy; fluorine-substituted compounds usually have high stability due to the very high dissociation energy of the C-F bond, and they are often good analogs because fluorine causes only a minor steric perturbation of the carbon skeleton.

In contrast to the classical approaches to fluorination, a radiofluorination method would require a reaction that is rapid, convenient, and efficient, even when the fluorination species are the limiting reagents; it must also be adaptable to available sources of fluorine-18. There has been a wide-spread interest in developing methods for fluorine-18 labeling that fulfill these requirements, and in this laboratory the characteristics of olefin halofluorination,[2] the process by which halogen-fluoride adds across a double bond (Scheme I), have been investigated to determine the potential of this reaction for fluorine-18 labeling. Although this reaction has been applied in many syntheses,[3,4,5,6] the key characteristics of importance to potential fluorine-18 labeling - namely, rate, yield, and efficiency when fluoride is limiting - have not been studied previously. In these studies, the halofluorination reaction has been optimized under conditions of limiting fluoride; optimization of the radiofluorination reaction is currently near completion.

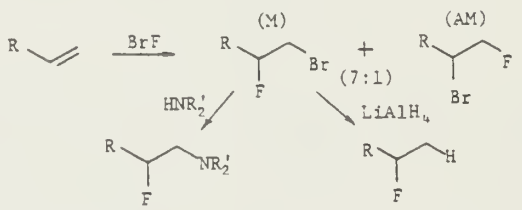
Scheme I



X = Cl, Br, I

Allylbenzene, 1-hexene, and propene were chosen as model substrates for the halofluorination reaction. Many parameters (solvent, temperature, various sources of fluoride and electrophilic halogen, and reactant stoichiometry and concentration) were found to have an important effect on the yield and rate of halofluorination. It was found that simple olefins undergo rapid bromofluorination when treated with 1,3-dibromo-5,5-dimethylhydantoin (DBH) and acidic sources of fluoride ion (HF/pyridine, aqueous HF, or $KF \cdot 2H_2O$ in the presence of acid) in methylene chloride, generally giving a 7:1 mixture of Markovnikov (M) and anti-Markovnikov (AM) adducts (Scheme II).[7] This reaction is rapid and efficient, giving yields of 50-90% based on fluoride as the limiting reagent.

Scheme II



The products can be reduced to the fluorohydrocarbon by debromination (R_3SnH or $LiAlH_4$), or they can be used to alkylate amines. The labeling by halofluorination, using F-18 produced in a water target [$^{18}O(p,n)^{18}F$],[8] has been achieved in reasonably high radiochemical yields, both under carrier-added and no-carrier-added conditions.[9] In addition to olefins, other potential substrates for the halofluorination reaction would be allenes,[10] acetylenes,[3b,11] and diazo ketones.[3a,12]

The ultimate objective of this research is to develop successful methodology for the synthesis of F-18 labeled steroid and neurotransmitter analog radiopharmaceuticals capable of <u>in vivo</u> assessment of hormone and drug receptors. Prospects for the utility of the halofluorination reaction in this regard look very promising.

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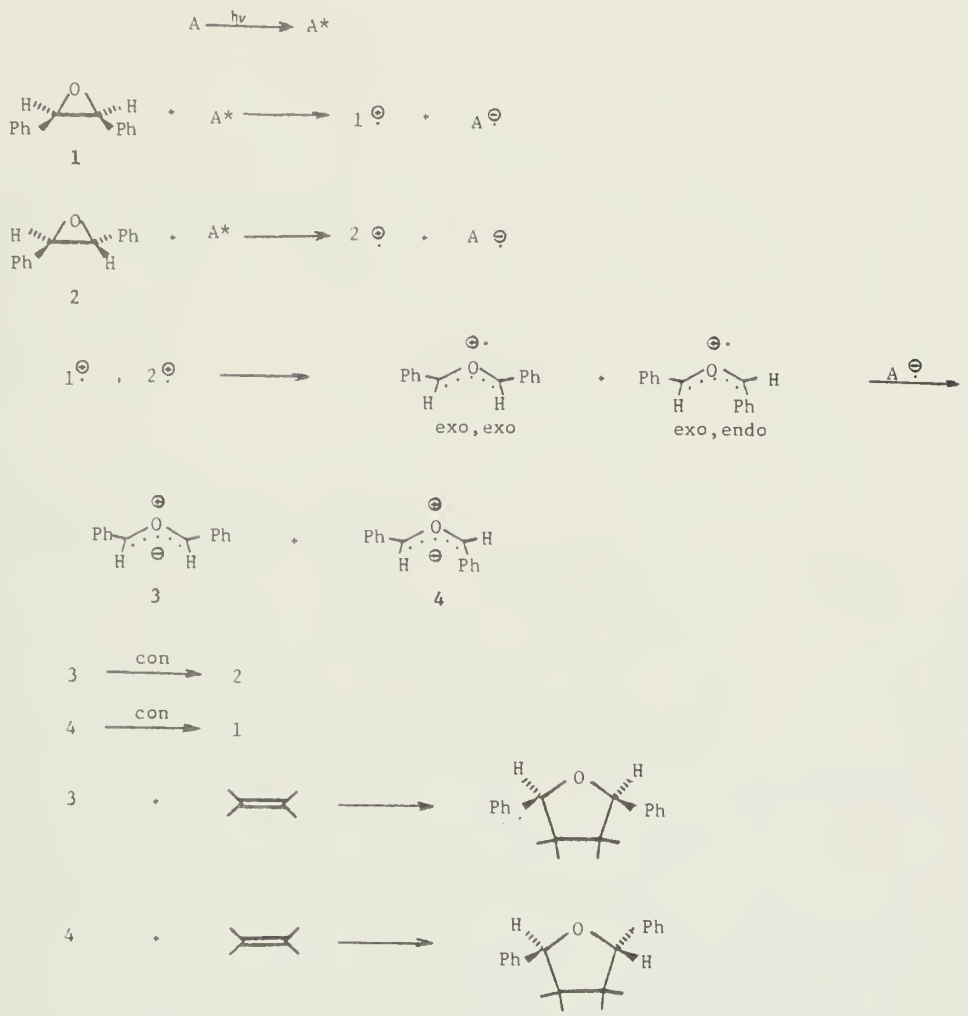
PHOTOSENSITIZED ELECTRON TRANSFER REACTIONS OF ARYLOXIRANES

Reported by John D. Wilkey February 25, 1985

The electrocyclic ring opening of oxiranes to carbonyl ylides has been known for some time, and has been induced by thermal activation, as well as direct and triplet sensitized irradiation. A relatively new point of entry into this class of 1,3-dipoles is via oxirane radical cations produced by electron transfer from the ground state of the oxirane to an excited state electron acceptor. The timing of back electron transfer from the acceptor and the role of orbital symmetry in the ring opening process are topics of current interest.

The first photosensitized electron transfer reaction of an oxirane was reported in 1978 by Arnold.[1] Upon selective irradiation of appropriate sensitizers in acetonitrile, photoisomerization of cis- and trans-2,3-diphenyloxirane (1 and 2, respectively) was observed. The reaction was relatively insensitive to solvent polarity, and yielded an identical mixture of oxiranes starting from either isomer. The sensitizer was not consumed in this reaction, and only sensitizers with sufficient singlet energy were capable of inducing reaction. Excitation of the sensitizer in the presence of oxiranes 1 or 2 and electron deficient alkenes yielded substituted tetrahydrofurans suggestive of a (4+2) cycloaddition of a carbonyl ylide and an alkene. The trapping of the carbonyl ylides by dipolarophiles competes effectively with ring closure, as no isomerized oxirane was detected during the irradiation. The ratios of isomeric tetrahydrofurans were different starting from 1 and 2. Triplet energy transfer from the sensitizer to the oxirane, and electron transfer from the oxirane to the triplet state of the sensitizer were ruled out as steps in the reaction mechanism. Based on ΔG values for electron transfer, calculated from the Weller equation, and results from fluorescence quenching studies, it was determined that the mechanism involved electron transfer from the oxirane to the singlet excited state of the sensitizer (Scheme I). The

Scheme I



oxidation potentials of the oxiranes indicate that the electron is donated from the phenyl moiety of the oxirane.[2] Subsequent intramolecular electron transfer, and nonstereospecific ring cleavage of $1^{+\cdot}$ and $2^{+\cdot}$ produce the ring opened oxirane radical cations. Back electron transfer from the sensitizer radical anion forms the isomeric carbonyl ylides, and thermally allowed conrotatory ring closure results in isomerization of the oxiranes. Tetrahydrofuran product ratios indicate that the ring opened oxirane radical cations are not formed equally from $1^{+\cdot}$ and $2^{+\cdot}$. Opening to the exo,exo conformation is favored by $1^{+\cdot}$ and $2^{+\cdot}$ over the exo,endo form. The exo,exo and exo,endo carbonyl ylides are not rapidly equilibrated thermally.[1]

An alternative explanation for the lack of stereospecificity in cycloadditions involving carbonyl ylides from radical cation precursors is suggested by theoretical calculations. Ring opening of the unsubstituted oxirane radical cation to the

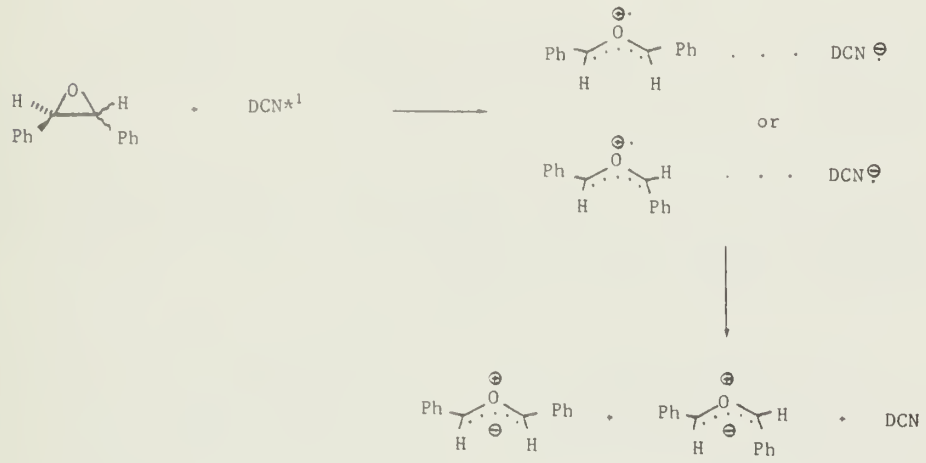
planar carbonyl ylide radical cation was found to be exothermic by ab initio SCF (with 4-31G basis set)[3] and MP2/6-31G*//6-31G*[4] calculations. The three electron electrocyclization was calculated to have a barrier to disrotatory opening of 3.7 kcal/mole and is formally forbidden.[4] The barrier to rotation around the C-O bond of the unsubstituted carbonyl ylide radical cation was calculated to be very low. Furthermore, substitution of oxirane with donors (e.g., NH_2) or acceptors (e.g., CN or Ph) was calculated to lower the barrier to rotation of the carbonyl ylide.[3] Similar effects upon the carbonyl ylide radical cation could allow interconversion of the exo,exo and exo,endo forms of diphenyl carbonyl ylide radical cation.

It is of interest to compare laser flash photolysis results of cis- and trans-2,3-diphenyloxirane under direct irradiation and electron transfer sensitized conditions. Thermal ring opening of 1 and 2 occurs in a conrotatory fashion, and photochemical ring opening in a disrotatory fashion, in accord with conservation of orbital symmetry.[5] However, there is evidence that Woodward-Hoffman rules apply less stringently to the photochemical process. Laser flash photolysis (266 nm) of 2 in acetonitrile affords a transient absorption spectrum (λ_{max} = 470 nm, τ = 780 ns) assigned to the exo,endo carbonyl ylide, based on orbital symmetry considerations. Similarly, photolysis of 1 yields the exo,exo carbonyl ylide (λ_{max} = 490 nm, τ = 100 ns).[6,7] In addition, 15- 20% of the symmetry forbidden exo,endo carbonyl ylide is formed from the cis- oxirane, presumably from the vibrationally unrelaxed electronically excited state of the latter.[7] The major pathway of decay of the carbonyl ylides is thermally allowed conrotatory ring closure to the oxirane, and activation parameters for this process have been determined.[6] Rate constants for reaction of these isomeric ylides reveal that they are equally reactive toward electron deficient dipolarophiles, indicating that product ratios accurately reflect the ratios of carbonyl ylides formed during the photolysis.[6]

Upon selective excitation (337.1 nm) of 1,4-dicyanoaphthalene (DCN) in the presence of 1 or 2, carbonyl ylides are produced which are kinetically and spectroscopically identical with those formed by direct irradiation.[8] The quenching of DCN fluorescence by oxiranes is known to occur via electron transfer from the oxirane to the singlet excited state of DCN.[1] However, the known absorption of DCN radical anion

(λ_{max} = 390 nm, $\varepsilon = 2.2 \times 10^4$ $M^{-1}s^{-1}$)[9] is conspicuously absent from the transient spectra, even in methanol or acetonitrile, indicating that no solvated radical ions are formed. Thus, back electron transfer from DCN radical anion to the oxirane radical cation to produce the isomeric carbonyl ylides is fast, and occurs within the photogenerated ion pair (Scheme II). The fraction of DCN singlet quenching events that give rise to carbonyl ylides is estimated to be close to unity.[8]

Scheme II



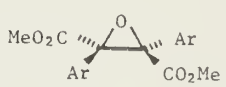
The mixture of carbonyl ylides obtained from either 1 or 2 is indicative of the relaxed symmetry control in the ring opening of oxiranes under electron transfer sensitized conditions. It appears that C-C bond cleavage occurs from the oxirane radical cation, giving rise to a mixture of carbonyl ylide radical cations. The ratio of exo,exo to exo,endo carbonyl ylides is different starting from each oxirane isomer, suggesting that neither a common intermediate nor an equilibrated mixture of these radical cations is involved. Assuming that the extinction coefficients of both carbonyl ylide forms are equivalent, both the cis- and trans- oxiranes prefer the formation of the exo,exo ylide to the exo,endo form (5:1 and 1.8:1, respectively).[8] Moreover, the enhanced preference of the cis- oxirane to form the exo,exo ylide relative to the trans-oxirane (2.8:1) is reflected in the tetrahydrofuran product ratios obtained by Arnold (3:1).[1]

Another study comparing direct irradiation and electron transfer sensitized laser flash photolysis results was carried out on oxiranes 5 and 6.[9] Both isomers undergo DCN sensitized

photoequilibration under steady state photolysis conditions; however, the intermediates could not be trapped either by electron rich or electron poor dipolarophiles. Laser excitation of DCN in the presence of 6 produces a transient spectrum assignable to $DCN^{-\cdot}$ (λ_{max} = 390 nm) and $6^{+\cdot}$ (λ_{maxs} = 390 nm and 580 nm). The radical cation of 6 is suggested to be a ring opened form, due to its lack of spectral similarity to the radical cation of p-methoxytoluene. The fraction of singlet quenching events that result in ion formation is small (0.3 ± 0.1). The decay of $6^{+\cdot}$ and $DCN^{-\cdot}$ fits well into second order equal concentration kinetics, indicating that back electron transfer from $DCN^{-\cdot}$ to $6^{+\cdot}$ is the dominant pathway for decay. Nevertheless, no transients attributable to ylides were observed. Cyclization to the oxirane of a short-lived ylide formed via back electron transfer could not be excluded. Direct flash photolysis of 6 likewise provided no evidence for ylide formation, but resulted in decomposition of the oxirane into a carbonyl compound and a carbene.



5



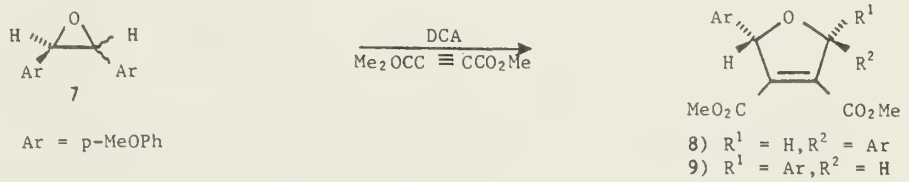
6

Ar = p-MeOPh

The transient absorption spectrum obtained from excitation of DCN in the presence of 5 shows an absorption at 460 nm which decays (over ~ 2 μs) into the spectrum obtained from 6. It was suggested that the absorption is due to the initially formed radical cation of 5 with the "hole" localized on one of the p-methoxyphenyl groups which subsequently decays, by intramolecular electron transfer, into the radical cation of 6. Alternatively, it was suggested that the species could be a ring opened radical cation of 5 which isomerizes to a more stable configuration (that of $6^{+\cdot}$).[9]

The instability of the carbonyl ylides from 5 and 6, evidenced by the inability to trap these intermediates with dipolarophiles, appears to be due to the introduction of carbomethoxy substituents.[10,11] 2,3-Bis(p-methoxyphenyl)oxirane (7) adds to dimethyl acetylenedicarboxylate upon electron transfer sensitization with 9,10-dicyanoanthracene (DCA) to give the 2,5-dihydrofuran adducts. It is interesting to note,

however, that sensitization by DCN, a better excited state electron acceptor than DCA, gives the C-O cleavage products, Ar_2CHCHO and $ArCH_2COAr$, which are also obtained from direct and triplet sensitized irradiation and thermolysis of oxirane 7.[10]

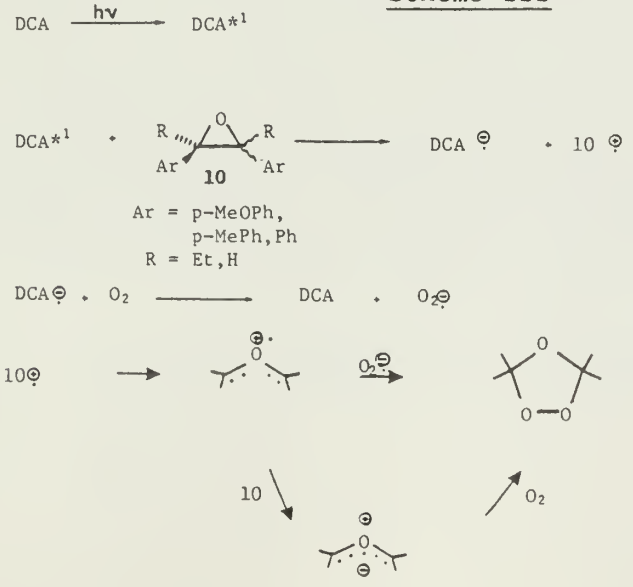


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8) $R^1 = H, R^2 = Ar$
9) $R^1 = Ar, R^2 = H$

An interesting application of electron transfer sensitized ring opening of oxiranes is the synthesis of ozonides from oxygen and epoxides. Ohta and co-workers have reported the formation of ozonides by electron transfer quenching of DCA^{*1} by electron rich 2,3-diphenyloxiranes 10 (i.e., oxiranes bearing p-methoxyphenyl substituents).[12,13] DCA^{*1} fluorescence is quenched by the oxiranes at a diffusion controlled rate, and the ozonides are produced almost quantitatively. Oxiranes with higher oxidation potentials (e.g., 2 and 2,2,3,3-tetraphenyloxirane) do not quench DCA^{*1} fluorescence and, hence, do not form ozonides under the reaction conditions. The quantum yields of ozonide formation from oxiranes bearing two p-methoxyphenyl substituents are greater than one, indicating a chain mechanism.[13] The proposed mechanism involves electron transfer from the oxirane to DCA^{*1} and formation of the ring opened radical cation which subsequently reacts with superoxide radical anion (from $DCA^{\cdot-}$ and O_2) to form the ozonide (Scheme III). The oxidation of a second molecule of 10 by the ring

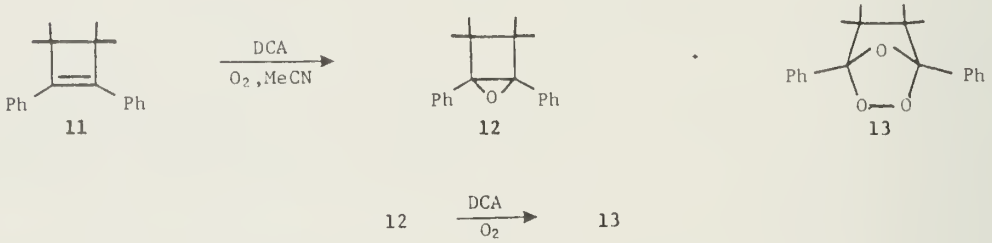
Scheme III



opened radical cation to generate a carbonyl ylide and a ring opened radical cation constitutes the chain propagation step. The carbonyl ylide may then react with molecular oxygen to form the ozonide.[13]

Griffin, on the other hand, has proposed that superoxide radical anion is not an intermediate in the electron transfer induced photo-oxygenation of oxirane 12.[14] DCA sensitized photo-oxygenation of 3,3,4,4-tetramethyl-1,2-diphenylcyclobutene (11) in acetonitrile produces, among other products, the oxirane 12 and ozonide 13 (Scheme IV). Oxirane 12 was proposed as the

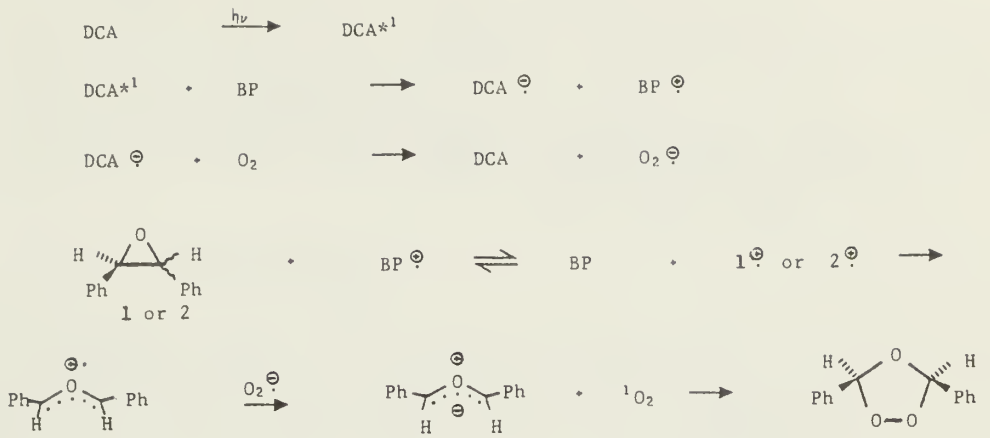
Scheme IV



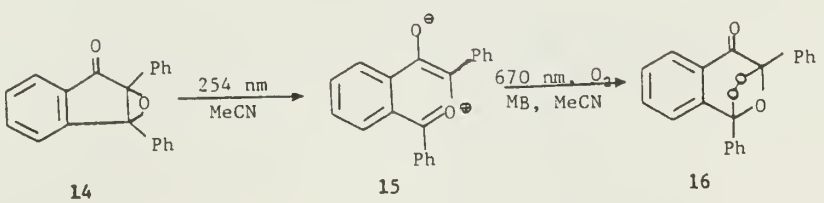
precursor to ozonide 13, and 12 has been shown to produce 13 in 94% yield under the reaction conditions. When the photo-oxygenation of 11 was conducted in the presence of benzoquinone, believed by Foote[15] to be an efficient $O_2^{\cdot-}$ trap, no alteration of the reaction course was observed. Thus, it was concluded that photo-oxygenation of 11 occurs via the carbonyl ylide of the initially formed oxirane 12 and oxygen, without the intervention of superoxide radical anion.

Schaap and co-workers have developed a method for the photo-oxygenation of compounds that have oxidation potentials greater than 2 V vs SCE and, consequently, do not quench the fluorescence of DCA^{*1}.[16,17,18,19] The addition of biphenyl (BP) as a cosensitizer permits the photo-oxygenation of oxiranes, cyclopropanes, and aziridines. The cosensitized mechanism of ozonide formation involves electron transfer quenching of DCA^{*1} by BP to give $BP^{+\cdot}$ and $DCA^{-\cdot}$ (Scheme V). Reversible secondary

Scheme V



electron transfer from the oxirane to $BP^{+\cdot}$ generates the oxirane radical cation. Although this second electron transfer is highly endothermic, the subsequent ring opening of the oxirane radical cation, and irreversible ozonide formation provide the driving force for the reaction. The longer lifetime of $BP^{+\cdot}$ compared to DCA^{*1} is also an important factor in the reaction mechanism. Only the cis- diphenyl ozonide was observed from the photo-oxygenation of 1 or 2. Similarly, the electron transfer photo-oxygenation of cis- and trans-2,3-dinaphthyloxiranes sensitized by DCA alone produced the cis- ozonide exclusively.[20] These results led Schaap to propose that the isomerization of the ring-opened oxirane radical cation to the more stable exo,exo form occurs prior to back electron transfer from $DCA^{-\cdot}$ (or $O_2^{-\cdot}$). That the carbonyl ylide could be trapped by singlet molecular oxygen was demonstrated in an analogous experiment.[19] Photolysis of 2,3-diphenylindenone oxide (14) produces the carbonyl ylide (15). Irradiation of 15 with visible light regenerates the oxirane. However, generation of singlet oxygen by Methylene Blue sensitization in the presence of 15 produces the ozonide (16) in 95% yield. The carbonyl ylide reacts with ground state oxygen, but at a significantly slower rate.



14 15 16

In conclusion, electron transfer sensitized reactions of oxiranes appear to proceed through the carbonyl ylides. Whether the mixtures of isomeric carbonyl ylides are formed via nonstereospecific ring opening of the oxirane radical cation, or by isomerization of the ring opened oxirane radical cation prior to back electron transfer, awaits further investigation on a faster time-scale.

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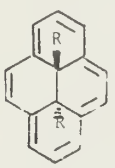
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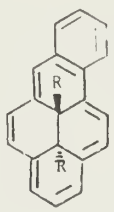
ANNELATED AROMATICS AND THE MILLS-NIXON EFFECT

Reported by Paul A. Keifer February 28, 1985

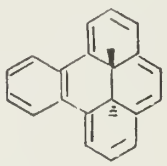
Ring currents due to delocalized π-electrons are prominent features in ^{1}H nmr spectra of conjugated cyclic molecules.[1] Annulenes are particularly useful in studying ring currents in that they can possess any ring current ranging from strong diatropicity (typical in [4n + 2] π-electron systems) to strong paratropicity (seen in [4n] systems) or any value in between. These different levels of dia- and paratropicity have been observed in ^{1}H nmr spectra of annulenes and correlated with various structural features, one of which has been benzannelation.[2] While several research groups have studied benzannelated aromatics,[3-7] Boekelheide and Mitchell and their coworkers have investigated benzannelation effects with an extremely useful [14]-annulene ring system. The parent compound, trans-15,16-dimethyldihydropyrene (1), not only contains a macrocyclic ring which is planar, but also contains internal substituents well buried in the π-electron cloud which provide sensitive probes to changes in the ring current.[8] Various mono- and dibenzannelated analogs of 1 (compounds 5 - 9) have been synthesized and studied by nmr, bond order calculations, and in some cases chemical reactivity.[9] The site



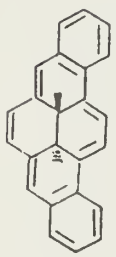
1 R = CH_3
2 R = H
3 R = CH_2CH_3
4 R = $CH_2CH_2CH_3$



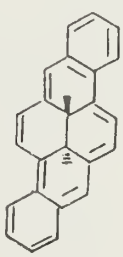
5 R = H
6 R = CH_3



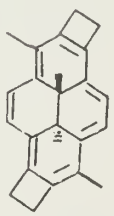
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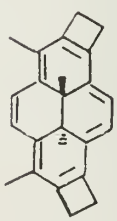
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9



10



11

of benzannelation was shown to affect the magnitude of the decrease in diatropicity; the decreased diatropicity is thought to be due to bond order changes within the macrocyclic ring. The synthesis of compounds related to 1 but bearing different substituents on the internal bridge (compounds 2 - 4) has allowed them to also probe the π-electron cloud itself.[10]

A related pair of substituted dimethyldihydropyrenes (10 and 11) was also synthesized to study the effect of fusing strained, saturated rings onto aromatic systems.[11] This was prompted by other reports, both experimental[12-14] and theoretical,[15,16] which have addressed the Mills-Nixon effect proposed in 1930.[17] Mills and Nixon hypothesized that strained cycloalkane rings, when fused onto benzene, caused partial π-bond localization While both sides of the Mills-Nixon effect issue have been supported by different kinds of experimental evidence,[18,19] Mitchell's results, in agreement with modern theories, indicate no significant localization of the π bonds.

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ELECTRON DEFICIENT CARBOCATIONS

Reported by James R. Ahlrep March 7, 1985

Carbocations as reactive intermediates in organic chemistry were not widely accepted until 1932.[1] Prior to this time, organic reactions, such as the pinacol rearrangement, which occur through carbocationic intermediates, were labeled as exceptions to the mechanistic rules of the time. However, following the acceptance of the concept of trivalent positively charged carbon, carbocations were found to be involved in a large assortment of rearrangements, elimination reactions, and substitution reactions of organic compounds.

Normally when a carbocationic intermediate is invoked in a reaction mechanism, the placement of the carbocation proximate to an electron withdrawing group is to be avoided. Indeed, solvolysis experiments have demonstrated that a cyano function β to an incipient carbonium ion center renders a rate retarding effect on ionization of 10^3-10^7.[2] A hasty extrapolation of this result could lead to the conclusion that carbocations α to an electron withdrawing group are extremely unstable or possibly nonexistent. However, such electron-deficient carbocations are known and some are surprisingly stable.

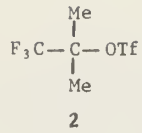
Electron deficient carbocations are defined as those species **1** in which the substituent R is less electron donating than



hydrogen.[3a-c] Carbocationic species in which R = $-CF_3$, -CN, -C(O)R, $-NO_2$[4], and $-PO(OR)_2$[5a-b] have been studied. This abstract will focus on recent research on electron deficient carbocations in which R = $-CF_3$, -CN, and -C(O)R.

Alpha-Trifluoromethyl carbocations

Early studies of carbocations generated α to a $-CF_3$ group concentrated on the triflates CF_3CMe_2OTf **2**[6a-b] and $CF_3CMeArOTf$ **3a-b**.[6a,7a-c] Solvolysis studies of **2** and **3a-b** and their hydrogen substituted analogs reported $k(H)/k(CF_3)$ ratios between 10^5-10^7 depending on the solvent.



2



3

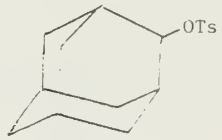
3a) Ar = p-ClC_6H_4

b) Ar = C_6H_5

-OTf = $-O-\overset{O}{\overset{\|}{S}}(=O)-CF_3$

This large rate ratio is consistent with the existence of a destabilized carbocationic intermediate, due to the presence of the strongly electron-withdrawing CF_3 group; however the rate ratio alone does not verify the existence of such an intermediate.

Further studies gave evidence that both **2** and **3a-b** underwent solvolysis via carbocationic intermediates; however, they appeared to react by somewhat different mechanisms as shown by the dependence of the solvolysis rate on the solvent employed. Good correlation, m = 1.03 and m = 1.09 respectively, between the rates of solvolysis of substrate **3a** and **3b** and the rates of solvolysis of 2-AdOTs was observed (2-AdOTs is used as a model of a system which reacts via a rate limiting reaction to form

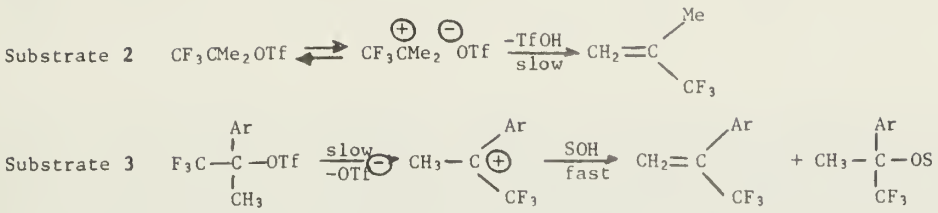


2-Adamantyl Tosylate
(2-AdOTs)

a carbocation). Substrates **3a-b** also exhibited modest increases in solvolysis rates, (10-30%), upon the addition of salts such as $NaClO_4$, NaOAc, NaCl, and NaN_3. This behavior parallels that of the 2-AdOTs system.

Solvolysis data for **2** did not correlate with that of the 2-AdOTs system. Triflate **2** instead was found to exhibit the behavior of the i-PrOTs system which initially forms an ion pair followed by a rate limiting elimination to give an alkene as the only product. In contrast, triflates **3a-b** , solvolyzing via a rate-limiting carbocation-forming step, produced both alkene and solvent addition products. Strongly nucleophillic anions from salts such as NaN_3 and NaOAc have a pronounced accelerating effect on the solvolysis of **2**. A rate increase of 2.9 was seen in a 0.06M NaN_3 solution. Similar rate enhancement is noted in the i-PrOTs system which solvolizes via the direct participation of added salts and solvents (a k_s process).

Solvolysis mechanisms of triflates 2 and 3a-b

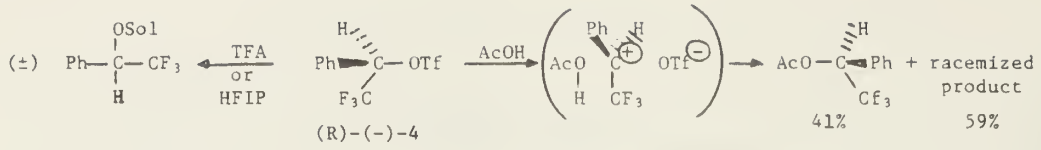


$k(CH_3)/k(CD_3)$ ratios for substrates **2** and **3a-b** also indicate the existence of carbocationic intermediates. For triflates 3a-b, $k(CH_3)/k(CD_3)$ ratios of 1.3 were found in strongly ionizing solvents and ratios of 1.6 were found in weakly ionizing solvents. Weakly ionizing solvents such as ethanol are unable to stabilize cationic intermediates, thus the demand for hyperconjugative stabilization increases with a resulting increase in the observed isotope effect.

The isotope effect, $k(CH_3)/k(CD_3)$, when one methyl group was deuterated in **2** was 1.8 regardless of solvent, but the effect increased to 3.8 upon deuteration of both methyl groups. This second result indicated a significant primary isotope effect since a ratio of only $1.8^2 = 3.2$ would have been expected if a non-carbocationic intermediate would have been involved. Thus, solvolysis and isotope effect data appear to support the conclusion that substrates **2** and **3a-b** solvolyse via mechanisms in which a large amount of carbocationic character develops in the intermediate.

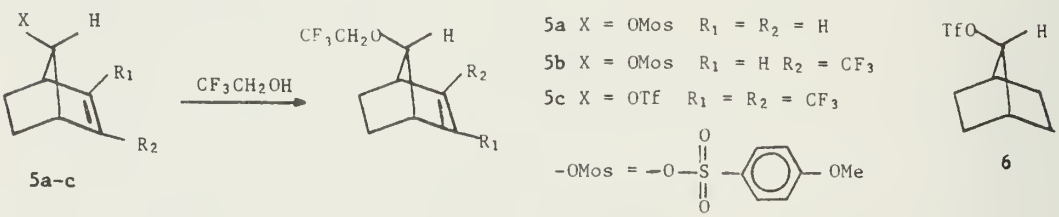
Attempts have been made to generate the carbocations of **2** and **3b** as stable species under superacid conditions. The carbocation $PhC^{\oplus}(CF_3)Me$ has been observed by NMR[8a-b] but attempts to generate and observe $CF_3C^{\oplus}(Me)_2$ have failed.[9] An attempt to produce $CF_3C^{\oplus}(Me)_2$ by the protonation of $CF_3CMe = CH_2$ also failed.[9]

Secondary systems of the type $ArCHOTsCF_3$ have also been studied.[10] Correlations with σ^+ gave values as high as -6.7 to -12 depending on the solvent. Direct evidence for the formation of carbocations in secondary systems comes from studies of optically active PhCH(OTf)Me **4**.[10] Solvolysis of **4** in highly ionizing trifluroacetic acid or $CF_3CH(OH)CF_3$ gave racemized product but solvolysis in strongly nucleophillic



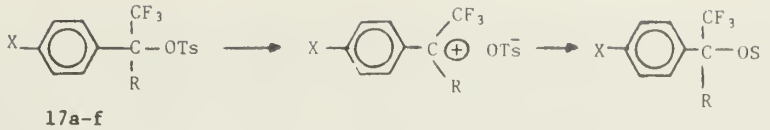
solvents such as ethanol and acetic acid gave products in which significant inversion had occurred. These results indicate that **4** undergoes rate limiting cation formation in less nucleophillic solvents, but in more nucleophillic solvents there is the formation of an ion pair which undergoes substantial substitution by solvent with subsequent inversion of configuration.

A recent study has noted the influence of the CF_3 group on a non-classical carbocation.[11] The solvolysis rates of **5a**, **5b**, and **5c** were 10^{12}, 10^6, and 1 respectively. These results present excellent evidence for the formation of a non-



classical (symmetrical) transition state involving the double bond. Interestingly, even **5c**, which solvolyses 17 times slower than **6** (in trifluroethanol), gave a solvolysis product which retained the starting stereochemistry. This result further supports the theory of double bond participation in the solvolysis of **5a-c.**

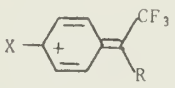
Doubly destabilized CF_3-substituted compounds have also been studied. Although long lived carbocations containing two alpha CF_3 groups have not yet been prepared, Astrologes and Martin have reported that the compound $PhC(CF_3)_2OTf$ solvolyzes in methanol via a carbocation.[12] The solvolyses of compounds **7a-f** have yielded results which indicate that a cationic intermediate may exist.[13] The $k(H)/k(CF_3)$ ratios for compounds **7a**, **7b**, and **7c** are quite small being 54, 2.4-5.2 (in different solvents),



17a-f

17a R = CF_3; X = H
b R = CF_3; X = $OMeCH_3$
c R = CF_3; X = F
d R = CN; X = H
e R = CH_3; X = H
f R = H; X = H

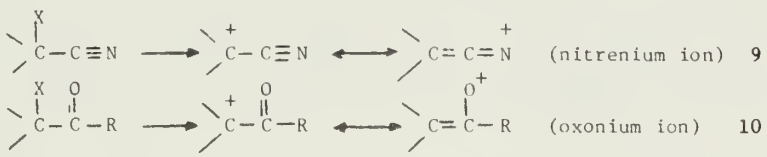
and 1.1 respectively. Since the rate ratio of a substrate containing only one destabilizing group ranges from $2x10^3$ to $2x10^7$ for CF_3 and 10^2 to 10^6 for CN, these "doubly destabilized" species are actually more reactive than the non-aryl substituted species. The aryl group's ability to delocalize the positive charge through the resonance structure **8** explains the observed enhanced reactivity of the doubly destabilized species.



8

α-Cyano Carbocations

In the substrates previously discussed, the solvolysis rate depression induced by the CF_3 group was due only to an inductive effect. However, substrates which contain a cyano group α to an incipient cationic center pose a more complex situation. The cyano and carbonyl groups, although both strongly electron withdrawing, are capable of considerable resonance stabilization of a carbenium ion through the resonance contributers **9** and **10**.[3b]

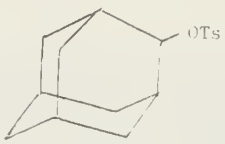


(nitrenium ion) 9

(oxonium ion) 10

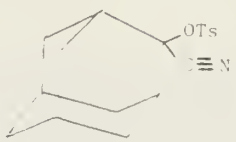
The first of these types of species studied were those which contained a CN group α to an incipient carbocation[14a-e]. Since a CN substituent β to an incipient cationic center was known to retard solvolysis by as much as 10^3-10^7 [2a-b], the probability of forming a carbocationic intermediate α to a CN group was considered to be low. Also, considering the Taft polar substituent constants, ($\sigma^*N\ CCH_2$ = 1.30, $\sigma^*CF_3CH_2$ = 0.92, $\sigma^*CH_3C(O)CH_2$ = 0.60), an α-CN group should inductively destabilize a carbocation even more than a CF_3 or a carbonyl

group. However, the β-CN group in compound **13** was reported to be 10^2 times more rate retarding than the α-CN group on substrate **12**. Although the α-CN compound reacted faster than



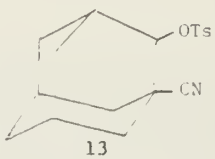
11

k_{rel} 1



12

10^{-}



13

10^{-5}

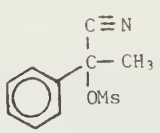
the β-CN compound, the α-CN rate was still much slower than the corresponding hydrogen substituted compound **11**.[14d,c]

In systems where the charge of the carbocation can be delocalized by neighboring group participation or by conjugation, k(H)/k(α-CN) ratios are much larger. For example, in **14** the ratio is 10^6.[14b]

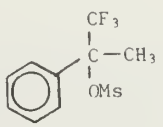


14

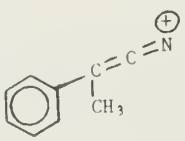
However, even if an aryl group is available for charge delocalization, the CN substituted compound still reacts faster than the corresponding CF_3 compound. Mesylate **15** was found to react $2x10^3$ times faster than **16** even though the CN group is more electron withdrawing than the CF_3 group. These



15



16

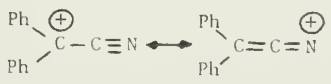


17

results seem to suggest that even in systems in which charge delocalization by aryl group(s) is possible, the charge delocalization by the CN group may still be important. The exact amount of charge delocalization by CN is unknown. Since the σ^+ <u>para</u> values for the CF_3 and CN groups are 0.61 and 0.66 respectively, and the ρ value for the solvolysis of **16** is -6.85 and the ρ value for the corresponding cyano substituted analog

15 is -6.70, the contribution of the resonance structure **17** would be expected to be insignificant.[15] Apparently, the balance between inductive destabilization and resonance stabilization of the CN group on a carbocation is dependent on the electron demand of the incipient carbocation.

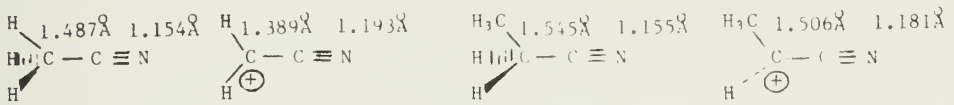
^{15}N NMR studies of cation **18** under stable ion conditions revealed evidence for the existence of resonance contributor **19**.[16] The ^{15}N peak of **18** was found to be a singlet at δ283, which was 30 ppm deshielded as compared to the neutral species. The deshielding observed was attributed to the carbon-nitrogen double bond character of **19**. In fact, the chemical shift of the ^{15}N in the cation is closer to that of an imine (δ318) than to that of the neutral compound (δ253). Since the ^{15}N peak was a singlet, the observed deshielding could not have been due to protonation of the nitrogen.



18 **19**

Theoretical studies of α-CN carbenium ions support the theory of CN delocalization of a positive charge.[17a-c]

STO-3G Calculation [17a]



20 **21** **22** **23**

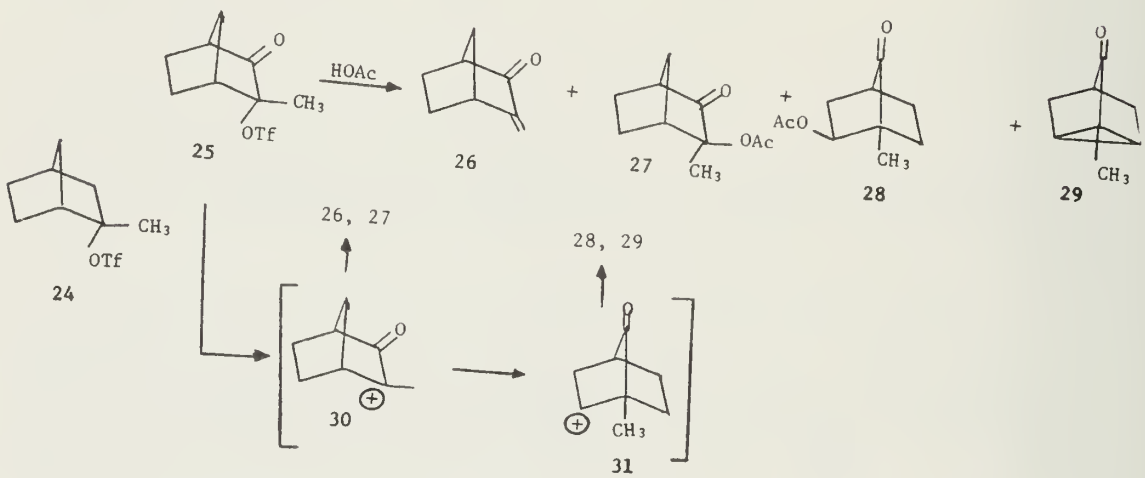
The C-N bond in cation **21** is calculated to be longer than the CN bond in the neutral species **20**. Also, the C-CN bond length becomes shorter as one goes from the neutral species to the cation. Both of these results are consistent with the delocalization of partial positive charge onto the CN group. As the C≡N bond loses some of its triple bond character due to the delocalized positive charge, it lengthens. Simultaneously, as the C-CN bond comes into conjugation with the C≡N group, it

shortens. A calculation of the orbital populations found that 0.25e was transferred from the C≡N bond to the empty p orbital in the cation.

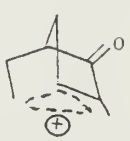
Only 0.15e was calculated to be transferred from the C≡N bond to the empty orbital in cation **23**. The decreased importance of the CN group in stabilizing cation **23** through delocalization is also noted in the calculation of bond lengths. Compared to the cation **21**, the cation **23** has a shorter CN bond and a longer C-CN bond as a result of the CH_3 group taking over the task of charge stabilization.

α-Carbonyl Carbocations

α-keto carbocations generated from α-keto triflates have been studied only recently.[18a-c] Norbornane **25** was found to solvolyse 10^7 times slower than **24**; however the products from the solvolysis of **25** indicate the intermediacy of a discreet α-keto carbocation.[18c]



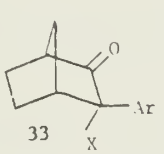
The formation of **26** and **27** indicated that the cation **30** exists long enough to undergo elimination and solvent capture. Products **28** and **29** were assumed to have arisen from a Wagner-Meerwein rearrangement of the classical ion **31**. The stereochemistry of the triflate group in **25** precludes a concerted Wagner-Meerwein rearrangement; however the possibility of a non-classical ion **32** was not ruled out.



32

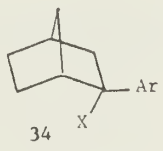
The beta-deuterium isotope effect for methyl d^3 **25** was found to be 1.47, one of the largest methyl d^3 isotope effects ever recorded.[18c] This large isotope effect should be expected since the very unstable carbocation requires a great deal of hyperconjugative stabilization.

A study of a series of α-aryl-substituted α-keto carbocations **33** found that $\rho^+ = -7.1$, compared to a $\rho^+ = +3.75$ for the non-carbonyl substituted aryl norbornane **34**.[18c] This



33

$\rho^+ = -7.1$

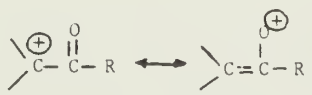


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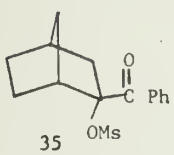
$\rho^+ = +3.75$

large ρ^+ value indicates that α-keto carbocations, even those in which delocalization by an aryl group is possible, are quite unstable.

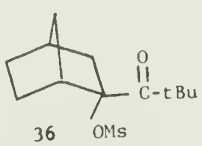
Although α-keto cations have been shown to be unstable compared to the corresponding hydrogen substituted compounds, there is evidence for stabilization of the carbocation through carbonyl delocalization.



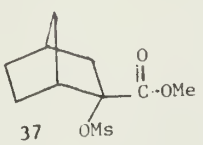
Creary has found evidence for carbenium ion stabilization by a carbonyl group in his studies on the norbornanes **35**, **36**, and **37**.[19] k(H)/k(α-CO) values for the preceeding compounds were



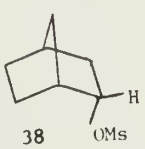
35



36



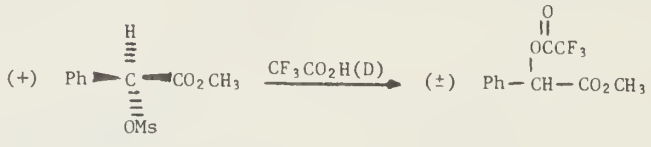
37



38

found to be 8, 0.3, and 76 respectively. Interestingly, **36** solvolysed 3.7 times faster than the hydrogen substituted compound **38**. mY_{OTs} values of 0.77 and 0.69 for compounds **35** and **36** indicate transition states with a considerable amount of cationic character.

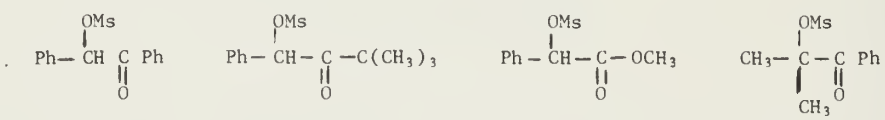
As further evidence for the existence of α-keto carbocations, a study of the solvolysis of optically active **39** in trifluroacetic acid yielded completely racemized product.



39 **40**

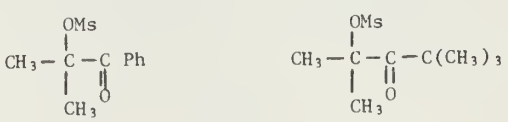
Enolization as a reaction mechanism was ruled out since solvolysis of **39** in CF_3CO_2D gave no deuterium incorporation in the product. Racemization of a chiral product was ruled out since (+) **40** completely retained its optical activity under the reaction conditions.[18b]

The mesylates **41-44** were also studied by Creary and were found to have $k_H/k_{\alpha\text{-}CO}$ ratios of 21, 13, 200, and 1.5 respectively.[19] mY_{OTs} values for **41** and **43** were 1.0 and 0.87 respectively. Both of these results imply that **41-44** solvolyze through a carbonyl-stabilized cationic intermediate.



41 **42** **43** **44**

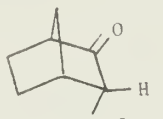
As further evidence for the existence of α-keto carbenium intermediates, the β deuterium effects in **45** and **46** were



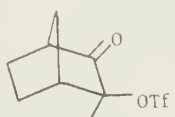
45 **46**

1.69 and 2.08 respectively.[19] These values are smaller than the isotope effect of 2.12 seen for isopropyl tosylate in trifluoroacetic acid. Isopropyl tosylate is known to solvolyze via a k_c process in trifluoroacetic acid. Thus, in **45** and **46**, there is no large demand for hyperconjugative stabilization due to the presence of carbonyl stabilization of the positive charge in the intermediate. If the carbonyl group were only inductively destabilizing, the β-d_6 effect would have been larger than 2.12.

Although tertiary α-keto stabilized carbocations appear to be quite stable, Creary has been unable to discover evidence for the existence of discreet non-aryl substituted secondary α-keto cations.[20] Substrates **47** and **48** exhibit exo/endo rate ratios of



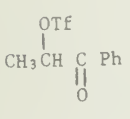
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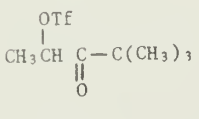
48

10^4-10^5. These ratios are much larger than the "normal" values of 10^2-10^3. Increased σ participation in the exo system due to the inductive destabilization of the α-keto group results in the abnormally large exo/endo rate ratio. The carbonyl conjugation was apparently insufficient to allow the formation of a discreet α-keto cation.

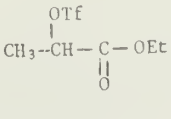
Studies of the triflates **49**, **50**, and **51** revealed that they solvolyzed via a nucleophillic mechanism.[19] As evidence for a k_s solvolysis mechanism, the relative solvolysis rates in



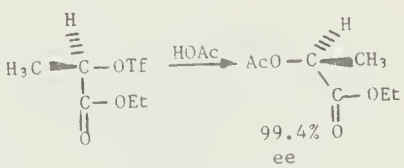
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50



51

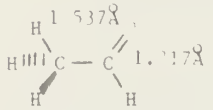


51 **52**

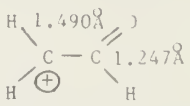
various solvents were ethanol > acetic acid > trifluoroacetic acid. The solvolysis of optically active **51** in acetic acid gave the inverted acetate **52** in 97.4% ee. Solvolysis of optically active **51** in formic acid gave similar results. Thus triflates **49**, **50**, and **51** appear to solvolyze via a k_s process, that is,

solvolysis assisted by solvent as the nucleophile. Apparently, the secondary α-keto cation is too unstable for a k_c, solvent unassisted, process to occur.

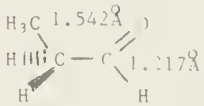
Theoretical calculations on the α-keto carbenium ion system indicate the presence of carbonyl delocalization.[17a-c] The C=O



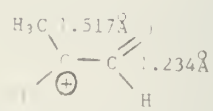
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54

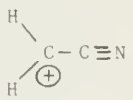


55



56

bonds in cations **54** and **56** lengthen in comparison to the C=O bonds in the neutral species. As partial positive charge delocalizes onto the C=O bonds, they weaken and consequently



57

lengthen. The C=O bond in **54** is shorter than that in **56** because in cation **56**, the cation is stabilized by the methyl group and so the need for carbonyl conjugative stabilization decreases.

α-CN groups have been calculated to stabilize carbenium ions more than α-keto groups. Less than 0.2 of a bond is transferred from the C=O bond to the C-C bond in cation **54**. By contrast, > 0.4 of a bond has been calculated to be transferred from the C≡N bond to the C-C bond in **57**.

In conclusion, species which react through relatively electron deficient carbocationic intermediates have been studied solvolytically and theoretical calculations of their structures have been performed. Carbocations containing alpha cyano or carbonyl groups are often quite stable, especially tertiary and benzyllic systems. Carbocations containing α-CF_3 groups are less stable than the corresponding carbonyl or CN analogs since the CF_3 group can act only as an inductive destabilizing group and is incapable of conjugative stabilization of the cation. Studies of systems such as these will lead to a more thorough understanding of carbocations.

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SOME RECENT SYNTHETIC METHODS FOR PREPARING ALLYLIC SILANES

Reported by James V. Gruber March 11, 1985

Allylic silanes are extremely useful intermediates in the formation of new carbon-carbon bonds. Their reactivity towards a wide range of electrophiles is well documented,[1] and reactions often proceed with excellent regio- and stereochemical control.[2]

There are three important features which make allylic silanes useful in organic reactions. First, unlike most metal allyls, allylic silanes do not undergo rapid 1,3-allylic shifts except at very high temperatures.[3] Secondly, silicon is able to stabilize a positive charge on a β-carbon atom. This stabilization effect is maximized when the Si-C bond is antiperiplanar to the vacant 2p orbital of the cation. Finally, silicon forms very strong bonds to oxygen and fluorine; thus, oxygen and fluorine nucleophiles can be used to cleave Si-C bonds.

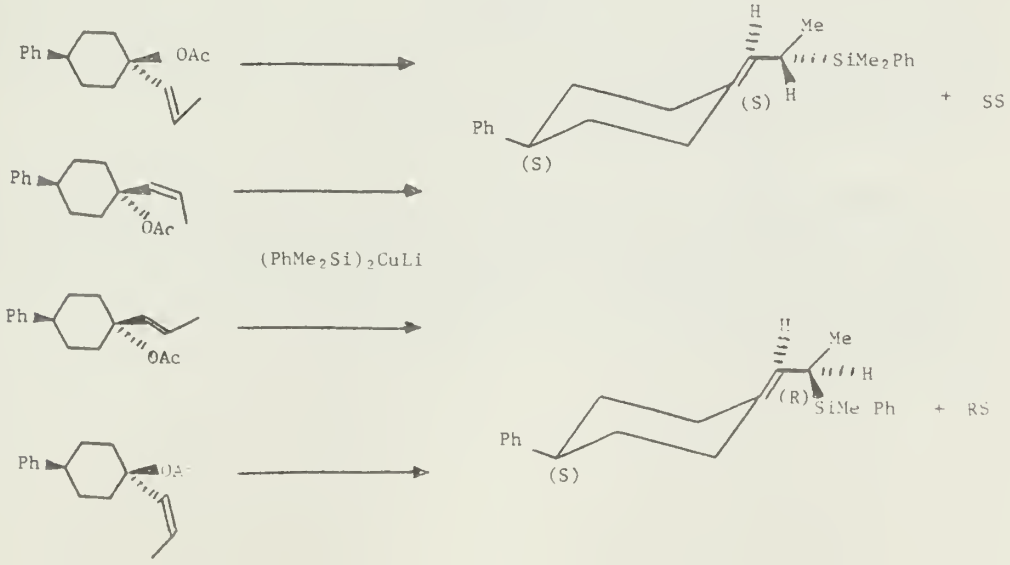
Because of the versatility of allylic silanes, new synthetic methods for preparing unusually functionalized allylic silanes, or for preparing allylic silanes with defined regio- and stereochemistry are important.

Allylic Silanes Derived from Reactions Using Silicon as a Nucleophile

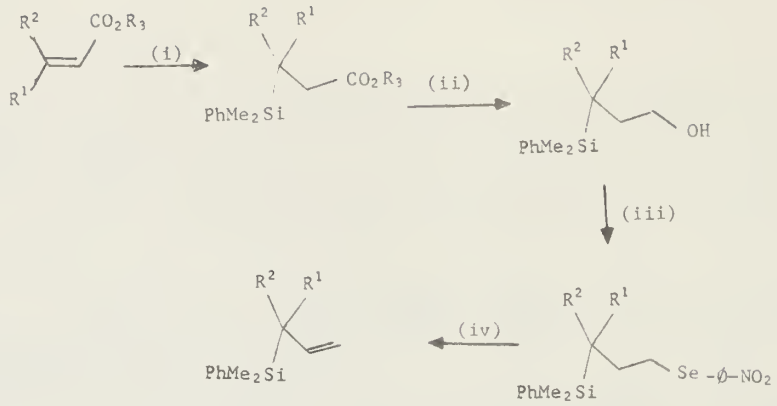
The use of silicon in the nucleophile provides increased control in regio- and stereoselectivity in the formation of allylic silanes over other methods which include the Wittig[4] and Diels-Alder reactions.[5]

Fleming and co-workers[6] have recently introduced bis(phenyldimethylsilyl)lithiocuprate as a source of phenyldimethylsilyl anion. They have studied addition of the reagent to cyclohexyl allylic acetates (Scheme I) and α, β- unsaturated esters (Scheme II).

Scheme I



Scheme II



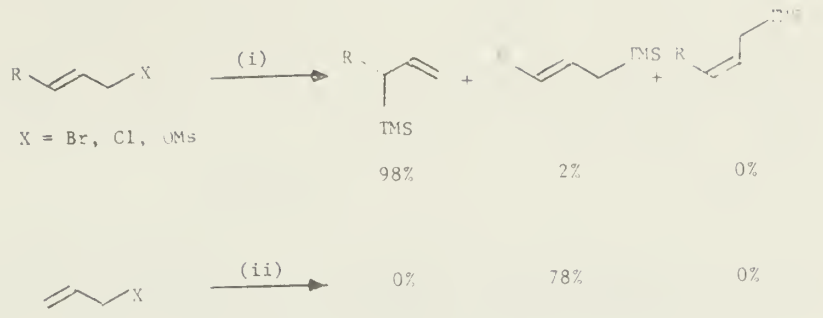
(i) $(PhMe_2Si)_2CuLi$ (ii) $LiAlH_4$, Et_2O (iii) $O\text{-}NO_2C_6H_4SeCN$, Bu^n_3P, THF
(iv) 50% H_2O_2

In order to study the regiochemistry of the S_N2' reaction of the silyl anion, the reactions shown in Scheme I were carried out. In all reported cases, the silyl moiety attacked anti to the acetate leaving group. The allylic silane products were then used to study the S_E2' reaction with a variety of electrophiles. The results indicate that electrophilic substitution of allylic silanes generally proceeds in an anti fashion regardless of other constraining factors in the ring system. Laycock, Kitching and Wickham[7] arrived at a conclusion similar to that of Fleming concerning the regiochemistry of the S_N2' reaction. They found that the use of CuI in their reactions improved the regiospecificity.

The experiments in Scheme II were significant: leading to allylic silanes in which the silyl moiety is found at the more substituted end of the allylic group. S_E2' reactions with these reagents place an electrophile at the less substituted end of the allylic group. This is an uncommon occurance in most allyl metal reactions as rapid 1,3-allyl metal shifts usually leave the metal at the less-substituted end of the molecule whereupon electrophilic substitution places an electrophile at the more crowded end of the molecule.[8]

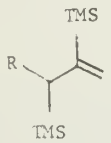
Other workers[9] have studied a series of regioselective reactions on simple linear allylic halides and mesylates using lithium trimethylsilyl anions. The regiochemical outcome could be drastically altered depending on whether or not CuI was present in the reaction mixture (Scheme III).

Scheme III

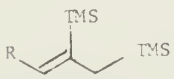


(i) TMSCuLi, HMPA/ET_2O, -60°C (ii) TMSLi, HMPA/Et_2O, -60°C

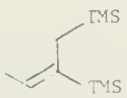
This methodology was used to form a variety of 2,3- bis(trimethylsilyl) alk-1-enes (**1a-c**). These little-studied species have some interesting unexplored theoretical and practical applications.



1a



1b

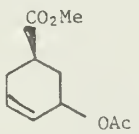
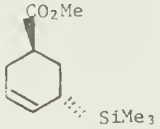
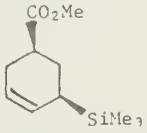


1c

Aluminum-silicon bonds, because of their more covalent nature, cause silicon to be a weaker nucleophile. In order for an aluminum-silicon reagent to act as a nucleophile towards an allylic electrophile, the latter generally must be activated by a transition metal catalyst. This decreased reactivity makes these reagents useful in reactions where a silyllithium reagent proves to be too harsh.

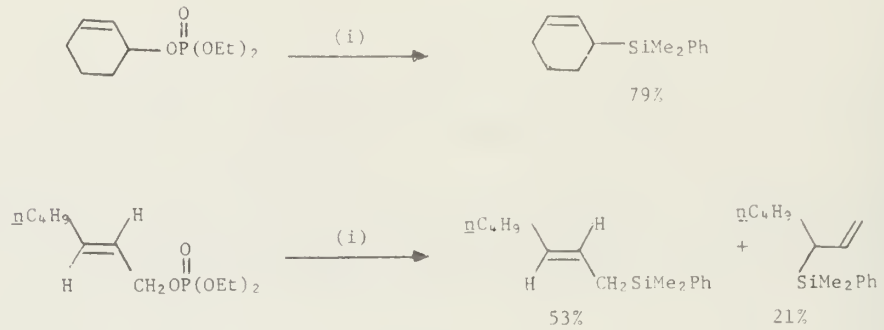
Recently, tris(trimethylsilyl)aluminum etherate has been used with allylic acetates activated by palladium and molybdenum catalysts.[10] The regiochemistry of the substitution reaction was dependent on the type of catalyst used. Net stereochemical inversion was obtained in the case of the Pd catalyst, but the Mo catalyst gave net retention (Table I).

Table I

Allyl acetate	Catalyst	Products		Yield, %
				
	a) $(Ph_3P)_4Pd$	75	25	56
	b) $Mo(CO)_6$	30	70	42

Workers at Kyoto University found that silyllithium reagents, used on allylic phosphates, would attack the phosphorous atom instead of the olefinic bond.[11] In order to overcome this difficulty, dimethylphenylsilyldiethylaluminum was used as the source of the silyl anion (Scheme IV).

Scheme IV



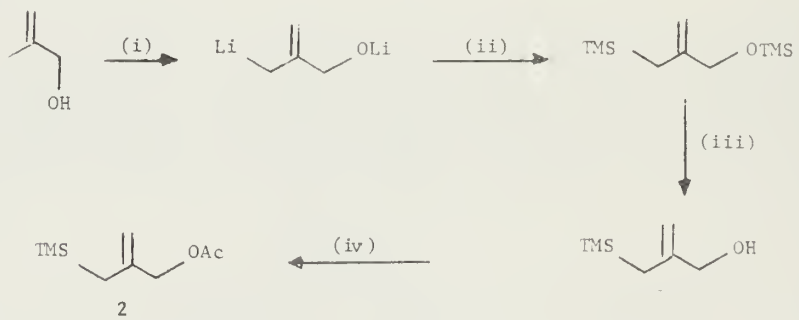
(i) $PhMe_2Si\text{-}AlEt_2$, THF, $0^{\circ}C$

Allylic Silanes Derived from Reactions Using Silicon as an Electrophile

Although the regiochemical and stereochemical outcome of the addition of an anion to a silicon electrophile are hard to predict, such additions are useful when unusually functionalized silanes are needed.

Trost and Chan[12] have recently developed an interesting allylic silane which has an adjacent silylophile on the γ-carbon, 2, (Scheme V).

Scheme V



2

(i) n-BuLi, Et_2O/TMEDA/THF, $0^{\circ}C$ (ii) Me_3SiCl (iii) 1N H_2SO_4, THF

(iv) CH_3COCl,  , CH_2Cl_2

The fact that 2 does not undergo self-annihilation allowed formation of trimethylene methane, 3, by using a palladium (0) catalyst. 3 can be used in [3+2] cycloaddition reactions with electron-deficient olefins.



3-Halopropenes can undergo lithiation adjacent to the halogen; quenching with trimethylsilyl chloride produces α-halogen substituted allylsilanes.[13] No other procedure for generating such intermediates is known. The use of these reagents in electrophilic substitution reactions yields products with vinyl halide substituents. These are versatile compounds for further functional group transformations.

A very interesting allylic silane can be obtained by reaction of lithium methylene cyclopropane--the conditions for the formation of which have only recently appeared in the literature[14]--with trimethylsilyl chloride in the presence of Pd(0) and Ni(0) catalysts, **4**. The versatility of this allylic silane has yet to be exploited in synthesis.[15]



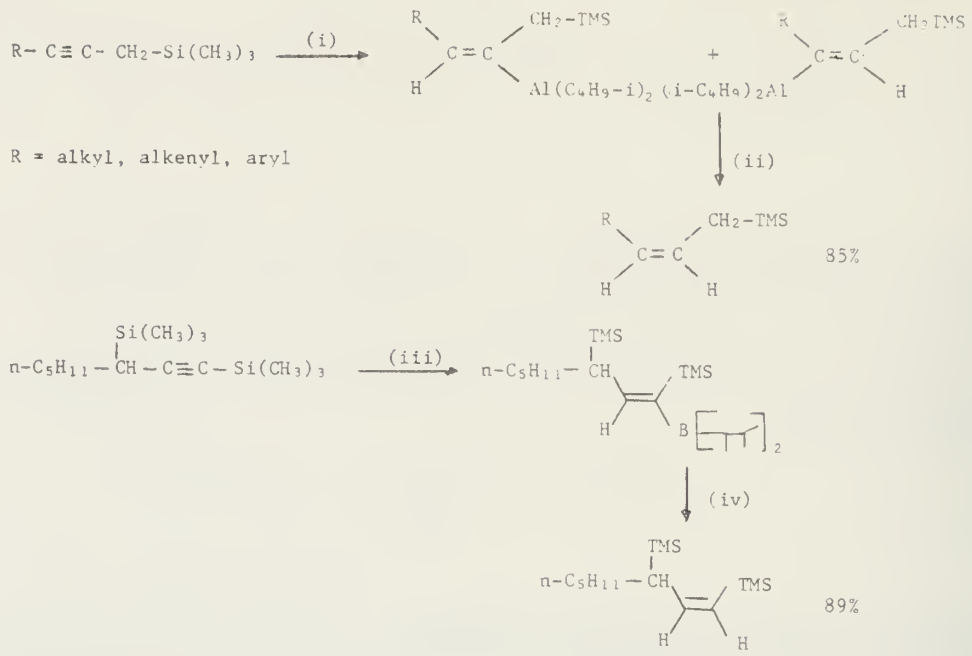
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Allylic Silanes by Reductive Methods

The preparation of allylic silanes by reductive methods can exhibit excellent regio- and stereochemical control. This compliments the nucleophilic substitution methods previously mentioned as a means of preparation of allylic silanes of known regio- and stereochemistry.

The hydroalumination and hydroboration of propargylic silanes yielded (Z)-1-trimethylsilyl-2-alkenes, (Z)-1,3-bis(trimethylsilyl)-1-alkenes, or 3-trimethylsilyl-1-alkenes depending on the starting material.[16] The reductive step in each case proceeded with excellent stereochemical control, but the intermediate alkenylalanes showed less regiochemical selectivity than the corresponding borane analogs. Hydrolysis of the metal intermediates gave exclusively the cis isomer in high isolated yields. In addition to forming useful allylic silanes, the alane and borane intermediates might also prove to be synthetically useful as vinyl metal reagents (Scheme VI).

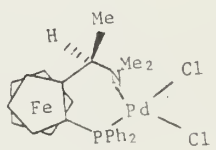
Scheme VI



(i) $(i\text{-}C_4H_9)_2AlH$, Et_2O, 40°C (ii) H_3O^+ (iii) HB[bicyclic]$_2$, THF, 0°C

(iv)(a) CH_3COOH, 65-70°C, (b) NaOAc, 30% H_2O_2, 35°C

The use of chiral phosphine palladium catalysts in hydrosilylation reactions has been explored. Recently, dichloro((R)-N,N-dimethyl-1-((S)-2-(diphenylphosphino) ferrocenyl) ethylamine) palladium (II), **5**, has been used as a chiral catalyst. Use of **5** in the

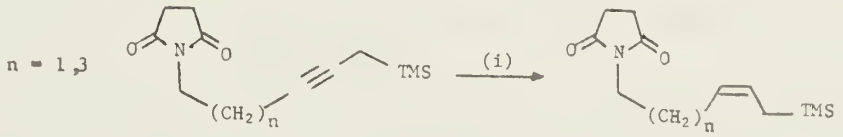


5

hydrosilylation of cyclopentadiene with dichloromethylsilane gave 3-(dichloromethylsilyl)cyclopentene with enantiomeric excesses as high as 25%.[17] The cyclopentyl allylic silanes thus produced were used to study the S_E' reaction in cases where the reactants are free of the stereochemical bias present in Kitching's and Fleming's work. Regardless of the absence of the stereochemical bias, addition of the silyl moiety to an electrophilic species proceeds in an anti-fashion. This evidence further supports the results obtained by Kitching and Fleming.

Hiemstra and Speckamp[18] have combined the cis-regiochemistry of poisoned catalytic hydrogenation with enhanced functionality to form the cis-trimethylsilylalkene imides shown below (Scheme VII). The synthesis

Scheme VII



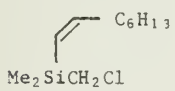
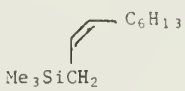
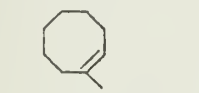
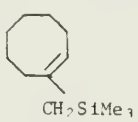
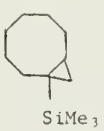
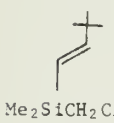
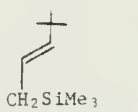
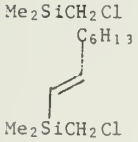
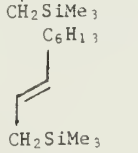
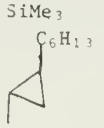
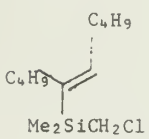
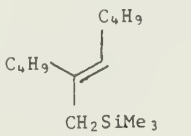
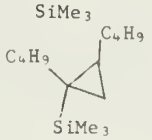
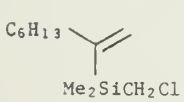
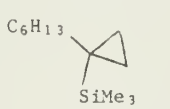
(i) H_2, 1.5 atm, $Pd/CaCO_3 \cdot Pb$

of allylic silanes from propargylic intermediates makes it possible to obtain them in isomerically pure states.

Miscellaneous Methods for Preparing Allylic Silanes

Investigation of the previously unknown Wagner-Meerwein-type rearrangement involving migration of an organic alkenyl group from silicon to the α-carbon has been examined.[19] Using six different alkenyl(chloromethyl)dimethylsilanes and treating each with a Lewis acid gave the allylic silanes shown below (Table II).

Table II

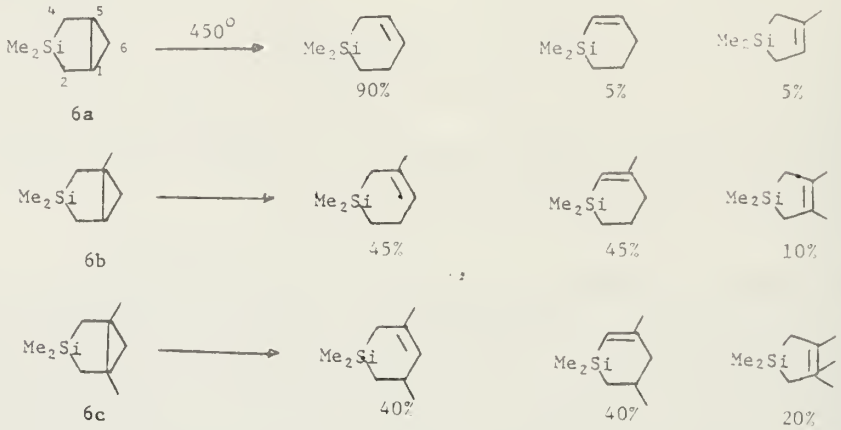
alkenyl(chloromethyl)silane	product(s)[a]	yield,%	allyl/cyclopropyl ratio
		89	100/0
	 	83	93/7
	 	65	87/13
	 	58	78/22
	 	93	77/23
		44	0/100

[a] After methylation

The stereochemical outcome of the rearrangement was primarily determined by the stability balance between α-silyl and β-silyl carbocations.

Manuel, Faucher and Mazerolles, in extending the work on the thermal rearrangement of bicyclo [3.1.0] hexane, looked at thermolysis of the analogous organosilicon derivatives, **6a-c**, (Scheme VIII).[20]

Scheme VIII



Thermolysis of **6a-c** in a flow system at 450°C yielded mixtures of compounds, containing silacyclohex-3-enes and silacyclopent-3-enes. It has been proposed that homolytic cleavage of the bridging C(1)-C(5) bond, or C(1)-C(6) bond produces biradical species which were shown to be the primary reactive species leading to all of the observed products. The silicon, through its d orbitals, was able to stabilize a radical in the α-position, thus explaining the predominant products in each case.

In conclusion, it would appear that the synthesis of allylic silanes of unusual functionalization, or of known isomeric composition is an active field. Recent methods have produced a variety of allylic and bis-silyl allylic silanes whose synthetic utility has yet to be realized. This will doubtless remain a very active topic for future work.

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SYNTHESES OF PENTALENOLACTONE AND PENTALENOLACTONE E

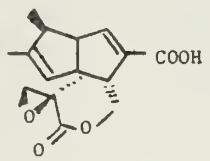
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Introduction

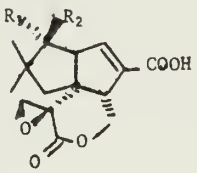
Since the isolation and identification of the sesquiterpene antibiotic pentalenolactone[1] (1), a series of structurally related metabolites, including pentalenolactone G[2] (2), H[3] (3), F[4] (4), E[5] (5), and P[6] (6), pentalenic acid[3] (7), deoxypentalenic acid glucuronide[4] (8) and the parent hydrocarbon itself, pentalenene[7] (9) have been reported (Scheme I). The antibiotic pentalenolactone has been found to have antibiotic activity against Gram-positive and Gram-negative bacteria as well as against pathogenic and saprophytic fungi.[1d] It has also been shown to have inhibitory activity against nucleic acid synthesis in bacteria cells.[1c] The antibiotic activity was found to proceed by blocking glycolysis in target organisms by selective inhibition of glyceraldehyde-3-phosphate dehydrogenase.[1e]

The structure and absolute configuration of pentalenolactone were firmly established by X-ray diffraction analysis of the bromohydrin derived from tetrahydropentalenolactone[1a,d] and by correlation with NMR and IR spectroscopic data.[1a,c,d]

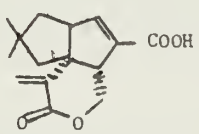
Scheme I



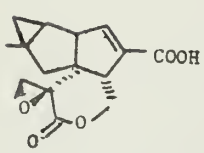
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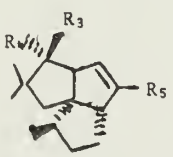
2 R_1R_2 = O
3 R_1 = OH, R_2 = H
4 R_1 = R_2 = H



5



6

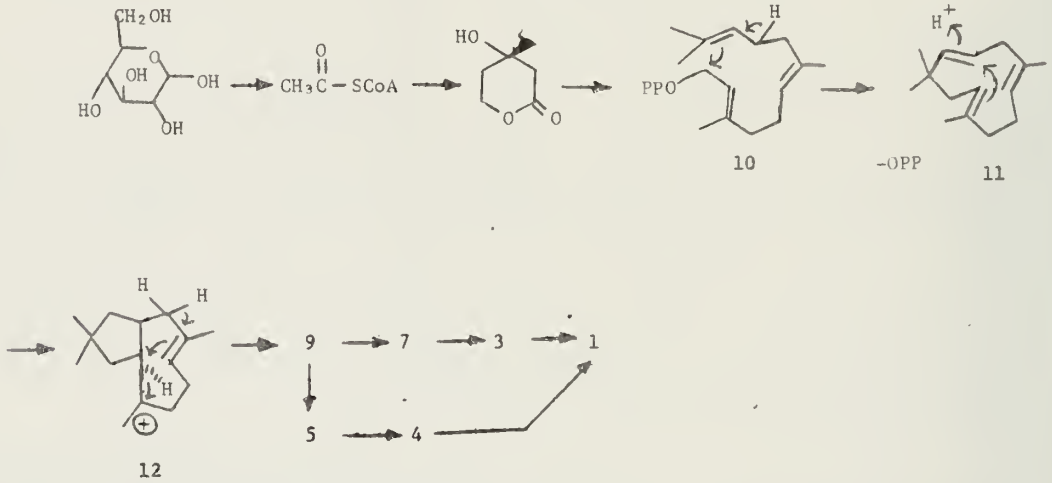


7 R_3 = H, R_4 = OH R_5 = COOH
8 R_3 = R_4 = H, R_5 = COO-1-glucuronyl
9 R_3 = R_4 = H R_5 = CH_3

The antibiotic properties of pentalenolactone served to elicit extensive investigation into its biosynthesis which has been established by Cane and co-workers by feeding [U-$^{13}C_6$]-glucose and [6-$^{2}H_2$]-glucose to the cultures of streptomyces UC 5319.[8,9,10]

The mevalonoid biosynthetic pathway of pentalenolactone involves the cyclization of farnesyl pyrophosphate (**10**) to humulene (**11**) followed by further cyclization via a protoilludyl cation[11] (**12**) to the tricyclic intermediate, pentalenene (**9**). Subsequent oxidative cleavage and rearrangement of pentalenene generates pentalenolactone (Scheme II).

Scheme II



Total Synthesis of Pentalenolactone

The highly compact tricyclic structure of pentalenolactone has attracted the attention of synthetic chemists. Two total syntheses of this natural product have been reported. This antibiotic possesses a tetracyclic ring system, including a diquinane backbone, a δ-lactone ring and a spiroepoxy ring α to the lactone carbonyl group. Incorporation of the four rings and the arrangement of its five chiral centers in the correct relative relationship are challenges to synthetic chemists.

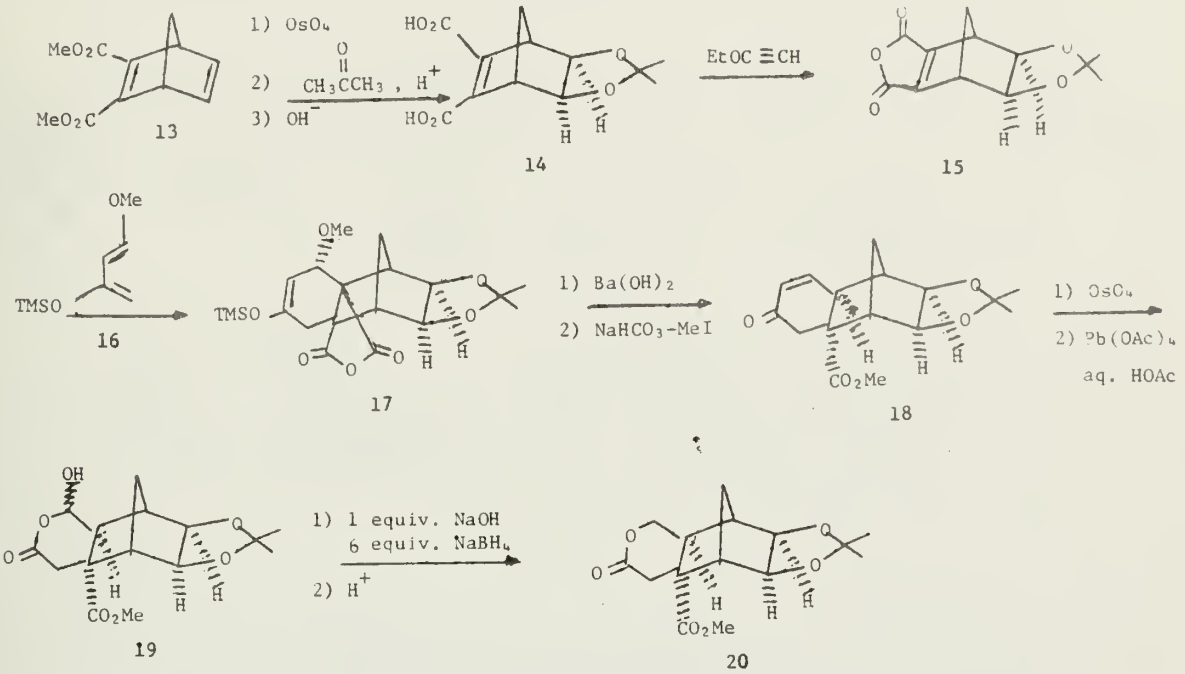
Diels-Alder Methodology

Danishefsky[12] and co-workers have reported the first total synthesis of pentalenolactone by an approach employing Diels-Alder reactions for the control of several key stereocenters and elaboration of the δ-lactone ring system.

Readily available compound **13** was converted to diacid **14** through oxidation with osmium tetroxide, acetonization and saponification of the diester group. Treatment of **14** with ethoxyacetylene afforded the anhydride **15** which underwent a Diels-Alder reaction with the diene **16** to give **17**. The cleavage of anhydride, unraveling of the β-methoxysilyl enol ether and decarboxylation of the vinylogous β-keto barium carboxylate were brought about by 1.2 equivalent of barium hydroxide to

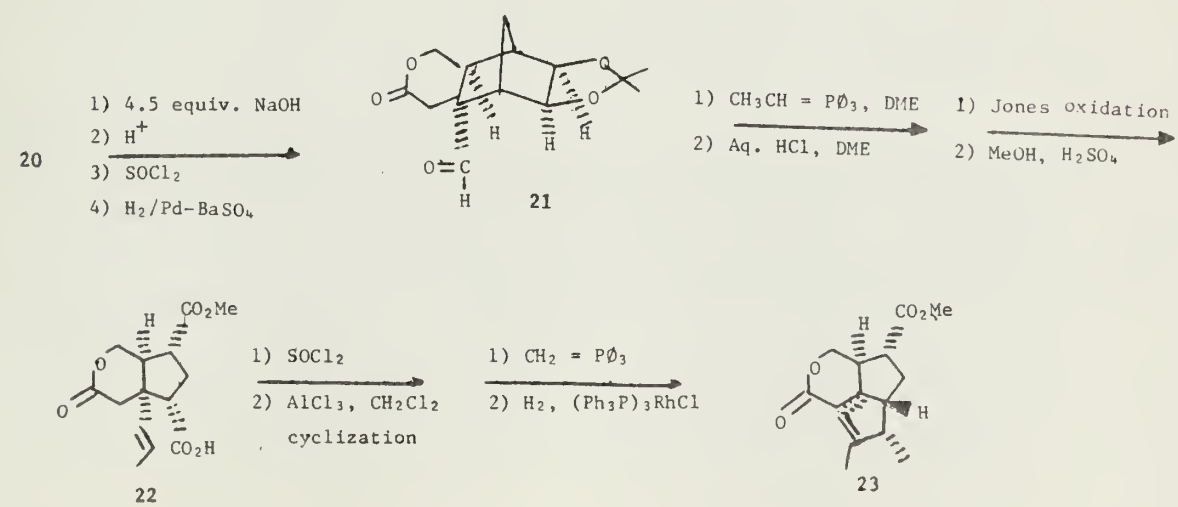
give an acid in one operation in 99% yield. Esterification of the resulting acid gave the ester **18** which is oxidized to the pseudolactone **19**. Treatment of **19** with one equivalent of sodium hydroxide containing excess sodium borohydride followed by acidification provided the δ-lactone methyl ester **20** (Scheme III).

Scheme III



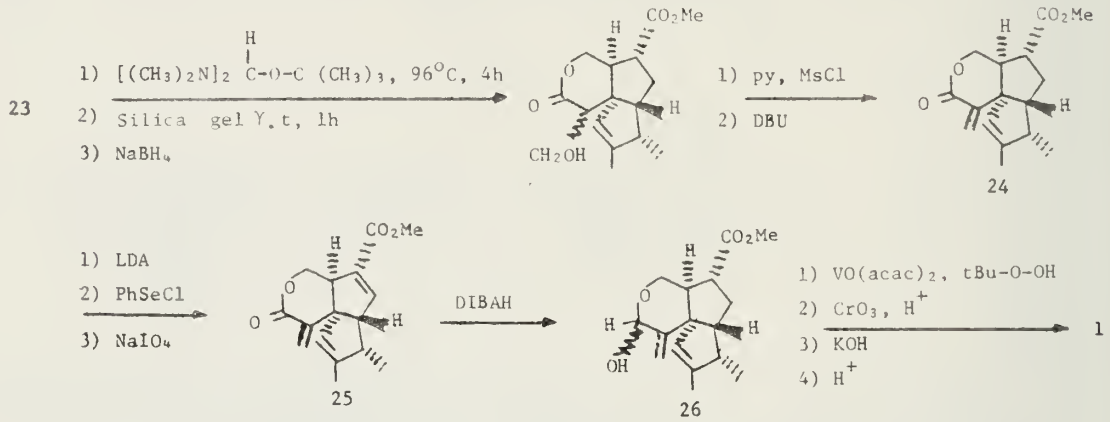
The stage was now set for the disconnection of the two-carbon bridge and the construction of the third ring. The ester **20** was converted to the aldehyde **21** which was further transformed to monomethyl ester **22**. Cyclization of **22** followed by olefination and hydrogenation gave endo-methyl lactone **23** as shown in Scheme IV.

Scheme IV



Introduction of the α-methylene group involved treatment of **20** with Brederic reagent and action of silica gel to give an enol which was reduced to an alcohol by sodium borohydride. Mesylation followed by elimination provided α-methylene lactone **24**. Base-induced selenenylation and oxidative deselenenylation afforded the deoxypentalenolactone **25** which was converted to the desired pentalenolactone as shown in Scheme V.

Scheme V



The α-facial epoxidation was achieved by reduction of the lactone moiety to the allylic hemiacetal **26** in which the hydroxy group might be disposed on the α face. Sharpless' epoxidation followed by Jone's oxidation, saponification and acidification afforded pentalenolactone. Starting with **13** and **16**, 33 steps were carried out to complete the synthesis in an overall yield of 0.2%.

Functionalized Diquinane Backbone

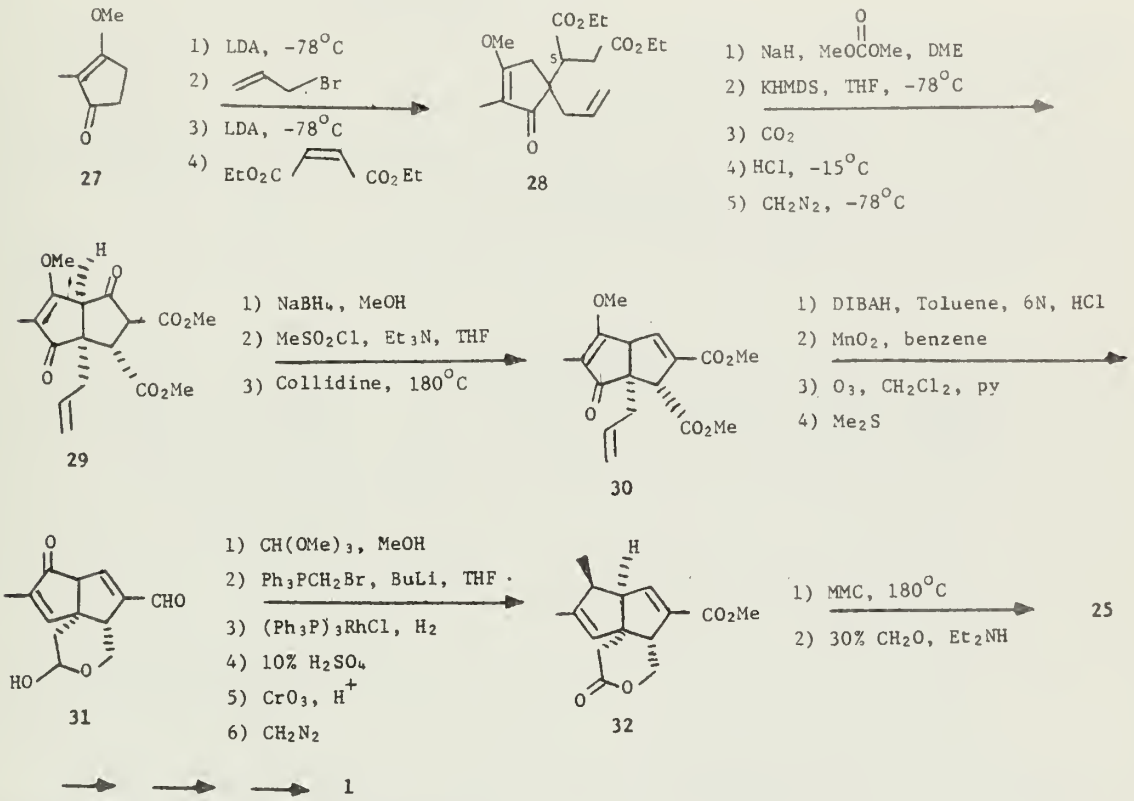
In their synthesis of pentalenolactone, Schlessinger[13] and co-workers employed selective acylation and alkylation of enolated ions to produce the diquinane framework appropriately functionalized for the introduction of the fused δ-lactone ring as shown in Scheme VI.

The cyclopentenone **27** was deprotonated twice and the enolates thus formed were selectively alkylated at the α' position to give **28** with 1:1 mixtures of epimers about C-5. Cyclization of **28** followed by carbonation with carbon dioxide, acidification and esterification gave the diester **29**. Reduction of **29** with sodium borohydride, mesylation of the resulting alcohol and elimination afforded the α,β-unsaturated ester **30**. Incorporation of the δ-lactone ring and introduction of the endo-methyl group were accomplished by a series of reactions, including diisobutylaluminum hydride reduction, manganese dioxide oxidation and

ozonolysis to provide the aldehydo-lactol **31**. Acetalyzation with methylformate and Wittig oiefination gave a diene which was subjected to hydrogenation followed by acetal hydrolysis, Jones' oxidation and esterification to give the lactone ester **32** as a 2:1 mixture of methyl group epimers at C-14(endo:exo = 2:1). Introduction of the α-methylene group was achieved most efficiently with methoxymagnesium carbonate followed by reaction of the resulting product with formalin solution to provide the deoxypentalenolactone **25**.

Since the conversion of **25** to **1** has been achieved by Danishefsky, the preparation of **25** constitutes the total synthesis of the natural product. The synthesis required 19 steps to produce **25** and the overall yield was 5.3%.

Scheme VI



Synthesis of Pentalenolactone E

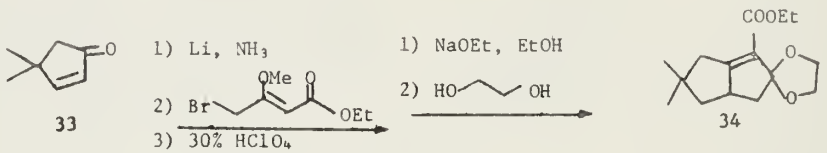
Pentalenolactone E shares the same common diquinane backbone and δ-lactone ring system as pentalenolactone. Instead of an α-epoxy functionality, however, pentalenolactone E possesses an α-methelene group. Two total syntheses and one biogenetic-like synthesis have been reported.

Intramolecular Michael Addition

Another approach to the δ-lactone ring system has been achieved by Paquette[14] and co-workers through the stereocontrolled lactone annulation in the total synthesis of pentalenolactone E. The key steps in their methodology involved kinetically controlled nucleophilic addition to an aldehyde carbonyl group and the ensuing intramolecular capture of the alkoxide function by a proximally positioned α,β-unsaturated ketone Michael acceptor.

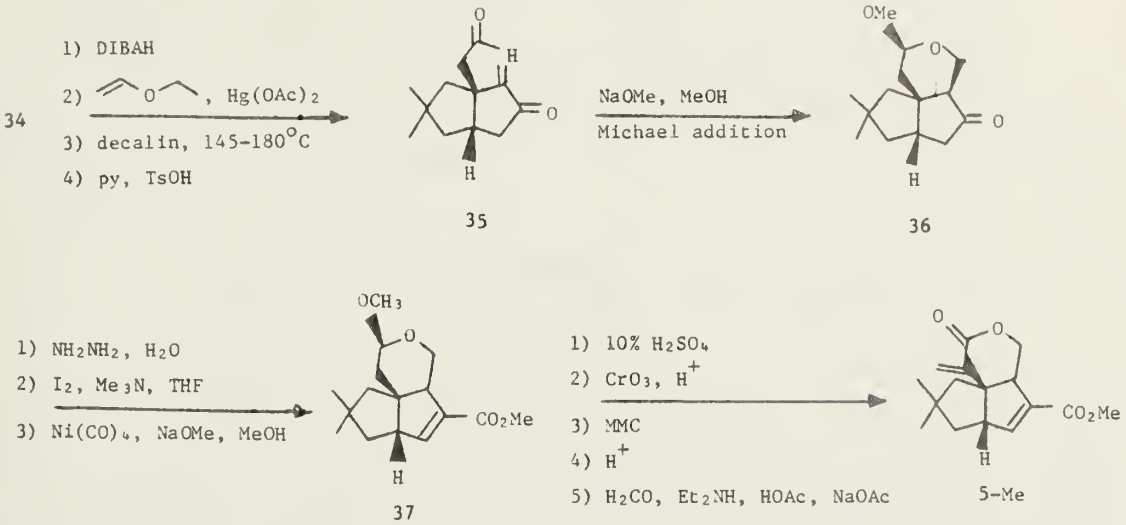
The diquinane framework was first constructed by reduction of 4,4-dimethylcyclopentenone (**33**) with lithium in liquid ammonia followed by regiospecific alkylation of the resulting enolate with ethyl 3-methoxy-4-bromocrotonate, then base-promoted cyclization and finally ketalization to give **34** as shown in Scheme VII.

Scheme VII



The protected carbonyl group in **34** allowed the controlled reduction of the ester functionality to an allylic alcohol. Formation of the vinyl ether of this alcohol followed by Claisen rearrangement and deketalization afforded the highly functionalized **35**. Chemospecific nucleophilic attack by methoxide ion at the aldehydo carbonyl group instead of the keto functionality and intramolecular Michael addition of the resulting alkoxide ion to the proximal enone system gave acetal **36**. Attention was now directed to the α,β-unsaturated ester functionality in the natural product. Conversion of **36** to hydrazone followed by iodine oxidation and the introduction of the carbomethoxy group through condensation with nickel carbonyl-sodium methoxide afforded the ester **37**. Acidic hydrolysis and Jones' oxidation followed by introduction of the methylene group α to the unmasked lactone functionality gave the methyl ester of the desired pentalenolactone E as shown in Scheme VIII.

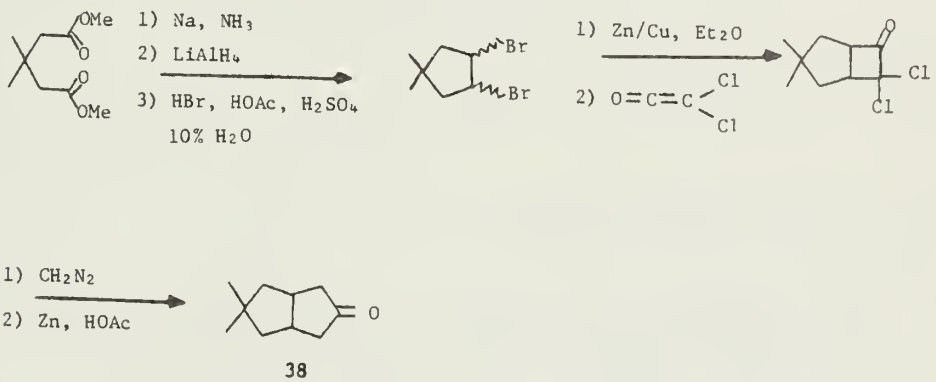
Scheme VIII



Intramolecular Carbene Insertion

The use of an intramolecular carbene insertion sequence to assemble the δ-lactone ring with complete stereochemical and high regiochemical control has been reported by Cane[15] and co-workers in their synthesis of the pentalenolactone E methyl ester. In their strategy, the symmetric bicyclic ketone **38** was the first target which was assembled in seven steps from dimethyl 3,3-dimethylglutarate as shown in Scheme IX.

Scheme IX

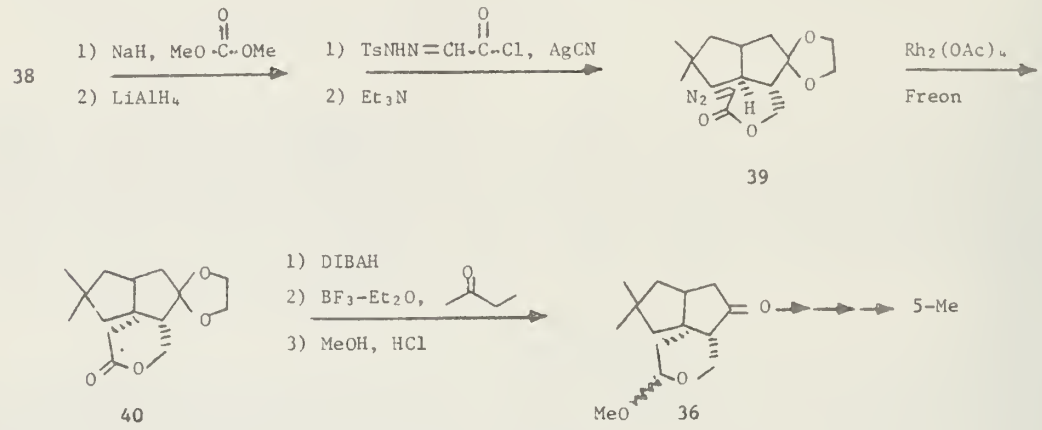


The carbene equivalent of the (diazoacetoxy)methyl group was then assembled at the α carbon of the carbonyl group in the exo-position. Intramolecular C-H insertion by the carbene species selectively provided the desired δ-lactone ring as shown in Scheme X.

Carbomethoxylation of **38** followed by ketalization and reduction of the ester group gave an exo-alcohol which was converted to the diazoacetate ester **39** through acylation with glyoxalyl chloride tosylhydrazone and base-catalized elimination. Ring closure by carbene insertion at C-1 bridgehead C-H bond generated the lactone **40**.

Reduction of the lactone, deketalization and treatment with acidic methanol afforded **36** which has been converted to pentalenolactone E methyl ester by Paquette. The synthesis was thus accomplished in 21 steps in an overall yield of 0.2%.

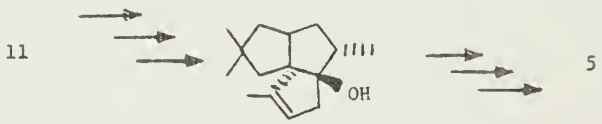
Scheme X



Biogenetic Like Cyclization of Humulene

Matsumoto and Shirahama[16] have also achieved the synthesis of pentalenolactone E methyl ester through biogenetic like cyclization of humulene. Humulene was first cyclized to an alcohol which was further transformed to the target molecule **5**.

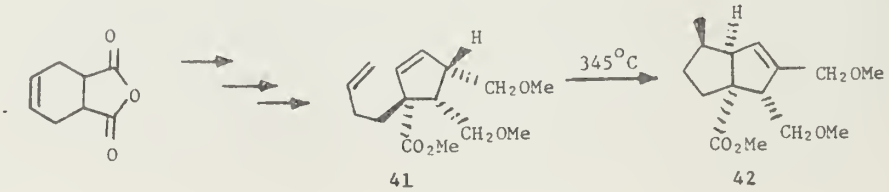
Scheme XI



Other Approach to the Tricyclic Ring System

In their studies toward the total synthesis of pentalenolactone, Heathcock and Plavac[17] took advantage of the highly stereoselective ene reaction (**41-42**) to provide the highly functionalized bicyclic compound **42** which might serve as an intermediate on the path to pentalenolactone (Scheme XII).

Scheme XII



Summary

Pentalenolactone makes a challenging synthetic target because of the compact tricyclic backbone, several asymmetric centers and the lactone ring system. Since the first total synthesis of pentalenolactone was reported, extensive synthetic studies have resulted in the elaboration of the lactone functionality in the diquinane framework. This class of sesquiterpene is attracting continuing synthetic investigation as well as biological evaluation.

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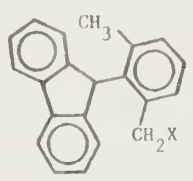
DIFFERENTIAL REACTIVITIES OF SOME CONFORMATIONAL ISOMERS

Reported by Tom Sowin March 18, 1985

Conformational analysis plays an important role in the elucidation of the physical properties and the chemical reactivity of molecules.[1] Non-rigid organic molecules are often presumed to be pure compounds even though they may exist in two or more predominant conformations which are interconverted rapidly in solution. However, conformational isomers may have very different reaction rates and yield different products. When conformational equilibration is fast relative to product formation, the ratio of products is determined by the difference in free energies of the transition states and independent of the position of conformational equilibrium.[2-3] On the other hand, when conformational equilibration in the starting material is slow or non-existent an understanding of such conformational reactivity is essential.

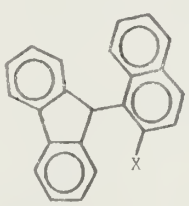
The investigation of conformational isomer reactivity is somewhat limited if conformer interconversion is rapid. Some researchers, therefore, have turned to the study of conformational isomers that possess high barriers of isomerization, in the hope that comparisons of the reactivities will produce useful information about those of rapidly exchanging systems.

Ōki and his coworkers have extensively studied the reactivities of the stable and isolable rotamers of 9-arylfluorenes of types **1** and **2**.[4] In most cases examined the ap isomer was less reactive than the sp isomer for S_N2 displacements,[5-7] oxidations,[8-9] reductions,[9] and Grignard additions.[9] The reduced reactivity of the ap isomer is primarily due to steric blocking of the reactive center by the fluorenyl ring system. However, the relative reactivities of the sp and ap isomers can be influenced by other factors such as cation chelation[10-11] and solvent effects.[12] Also studied were the differential reactivities of the diastereomeric methyl groups in 9-tert-alkyltriptycenes of type **3** in radical halogenation reactions.[13-14]



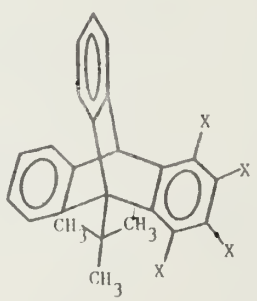
1

X = H, halide



2

X = methyl, methoxy, aldehyde, ketone, carbinol



3

X = H, halide

Differential conformer reactivity is also exhibited by ortho-tolyl-di-t-butyl-carbinols.[15] In acid-catalyzed dehydration reactions the ap isomer reacts 10^4 times faster than the sp form, mainly due to differences in ground state steric strain between the two isomers. Other examples of compounds that show different reactivities of conformational isomers include 2',6'dialkyl-2-halo-N-methylacetanilides,[16] humulene 9,10-epoxides,[17] and tetrahydro-1-naphthoquinols.[18-19]

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SYNTHESIS OF VICINAL DIAMINES

Reported by De-Kai Loo March 21, 1985

The vicinal diamino group is incorporated in many naturally occurring compounds and medicinal agents. Surprisingly, few general methods exist for the preparation of this group. The purpose of this report is to review the methodology for the synthesis of vicinal diamines with an emphasis on recent developments.

About a decade ago, most synthetic approaches were only the extensions of procedures developed to introduce a single amino moiety, such as displacement reactions with azides[1] or amino groups[2] or the Curtius rearrangement[3] (vide infra). Because of limitations and disadvantages of these methods chemists have sought new methods to synthesize this important group. These new synthetic approaches include stereocontrolled synthesis of unsaturated vicinal diamines from the Diels-Alder adducts of sulfur dioxide bis(imides)[4], cobalt-based methods for 1,2-diamination of alkenes[5], stereoselective synthesis from olefins and cyanamide[6], and a method based on the synthesis of imidazolidinone derivatives and their ring opening[7] (vide infra).

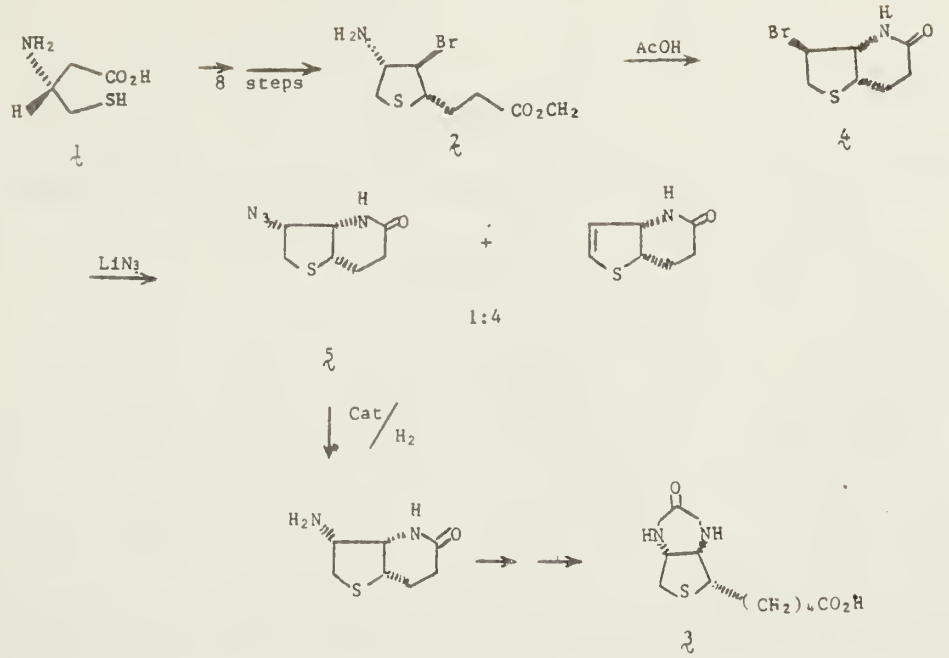
A. Classical Approaches

Displacement reactions

The first vicinal diamine compound 1,2-diaminoethane was synthesized by the reaction of vicinal dihalide with ammonia a hundred years ago.[2a] Unfortunately, this method was only useful for two or three carbon units. Ammonolysis of vicinal dihalides containing more than three carbon units yielded principally elimination products.[2b] With certain structures, however, ammonolysis of vicinal dihalides bearing more than three carbons gave excellent yields. An example was treatment of meso-dibromosuccinic acid with benzylamine to produce 1,2-dibenzylamino-succinic acid in 91% yield.[2a]

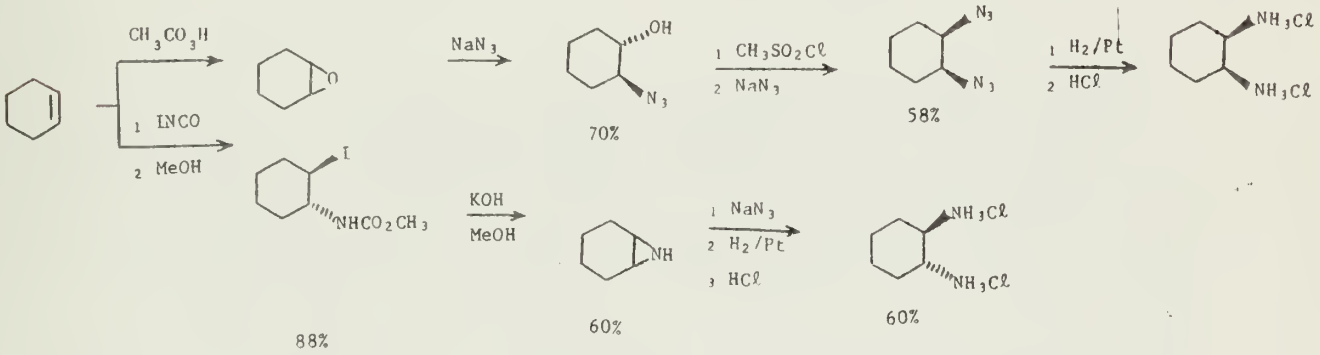
Azides have often been used as nucleophilic synthons for the amino group. Recent examples are found in synthesis of biotin. In 1975 Confalone and coworkers[1b] reported the total synthesis of d-biotin **3** from its biogenetic precursor L-(+)-cysteine **1** as shown in Scheme I. The amino bromide **2** was converted to trans bromolactam **4**, which underwent nucleophilic displacement with lithium azide to afford the desired azido lactam **5**, however, the unwanted elimination product was predominant. The azido lactam **5** was subjected to catalytic hydrogenation, hydrolysis, phosgenation, and extension of the side chain by two carbons to give the final product **3** in very low overall yield.

Scheme I



In a study of the aziridine ring opening by azide, Swift and Swern[1c] used stereospecific reactions to exert control over the stereochemistry of the product. For example, stereospecific nucleophilic opening of the epoxide and aziridine ring, as shown in Scheme II, provided cis- and trans-1,2-diamino cyclohexanes. In the case of acyclic olefins, the same stereospecific synthesis was achieved. Thus, cis-

Scheme II



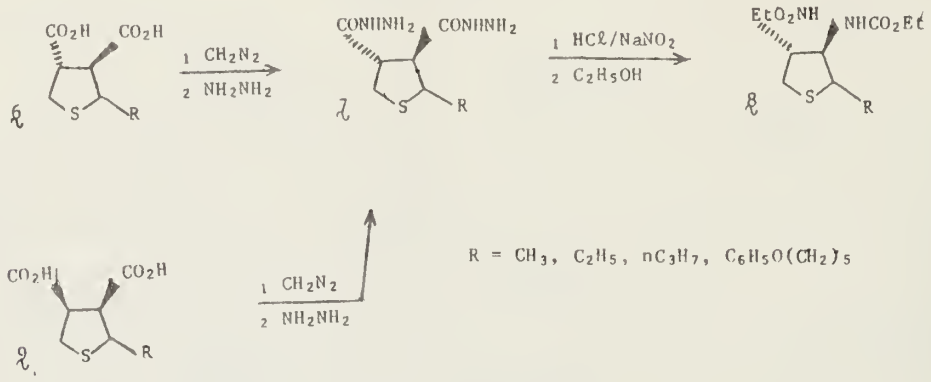
4-methyl-2-pentene was carried through the epoxide route to give erythro diamine in 28% overall yield and the trans isomer gave the threo diamine in 23% overall yield. The cis- and trans-4-methyl-2-pentene were carried through the aziridine route to give threo diamine in 14% and erythro diamine in 11% overall yield, respectively. As we can see, the yields are not good, especially in the case of the aziridine route.

Curtius rearrangement.

Another recent biotin synthesis provides an example of the synthesis of a 1,2-diamine via the Curtius rearrangement. Baker, Querry, Safir, and Bernstein[3a] first prepared the thiophane-cis-, trans-3,

4-dicarboxylic acid in five steps in overall 2-14% yield from ethyl thioglycolate and α,β-unsaturated ester. The trans dicarboxylic acid **6** was converted via the methyl ester to the trans dihydrazide **7**, which

Scheme III



R = CH_3, C_2H_5, nC_3H_7, $C_6H_5O(CH_2)_5$

was in turn degraded by a double Curtius rearrangement to the trans diurethan **8** (Scheme III). The trans diurethan could also be prepared by treating the diacid chloride of **6** with sodium azide. However, when the methyl ester of the cis dicarboxylic acid **9** was treated with hydrazine no cis dihydrazides could be isolated. Instead, inversion to the trans dihydrazide **7** took place. It seems that the hydrazine is sufficiently basic to cause epimerization. Such isomerization during hydrozinolysis of vicinal diesters also occured in other cases.[3b,c] The diacid chloride-sodium azide procedure could not be applied to the cis diacid which was converted to anhydride on treatment with thionyl chloride; use of PCl_5 gave only dark tars.

Other Classical Approaches to Vicinal Diamines.

Synthesis of vicinal diamines via intramolecular cyclization,[8] from selected starting materials,[9,10] using organometallic compounds, such as organoosmium (VIII)[11] (vide infra), organopalladium[12] (vide infra), thallium acetate,[13] and mercury (II) oxide[14] were also reported. In many cases the overall conversion to the desired vicinal diamine compounds occured in low yield, with little or no stereochemical control Despite these limitations, the greatest disadvantage of most classical methods was that they required organic starting materials which were not readily accessible.

B. Recently Developed Approaches

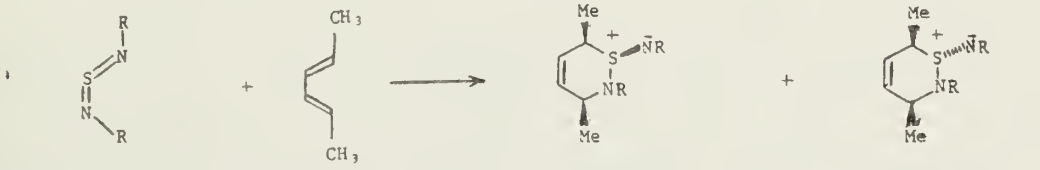
Because of the limitations of the classical approaches to synthesis of vicinal diamines, new methods of synthesis of this important group have been reported recently.

Stereocontrolled Synthesis of Unsaturated Vicinal Diamines

A methodology for the preparation of unsaturated vicinal diamines which allows total control of both relative conformation and double bond

configuration was reported recently by Natsugari, Whittle, and Weinreb[4]. Bis(imides) of sulfur dioxide reacted with 1,3-dienes in Diels-Alder fashion to produce 3,6-dihydrothiazin-1-imines. Thus, N,N'-di-p-toluensulfonyl sulfodiimene **10a** reacted with (E,E)-2,4-hexadiene at room temperature to give a mixture of adducts **11** and **12** in a ratio of 1.1:1 in 91% yield, as shown in Scheme IV. The configuration and conformation of the adducts as shown in Figure 1, were established by single-crystal

Scheme IV



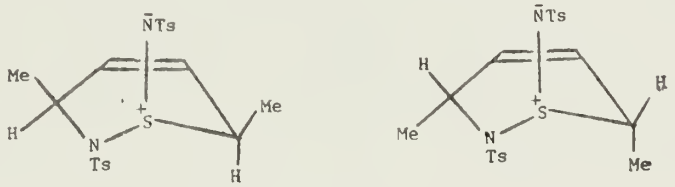
10a R = Ts
10b R = CO_2CH_3

11 R = Ts
13 R = CO_2CH_3

12 R = Ts
14 R = CO_2Me

X-ray analysis.[4] The Diels-Alder reaction of bis(carbamate) **10b** with

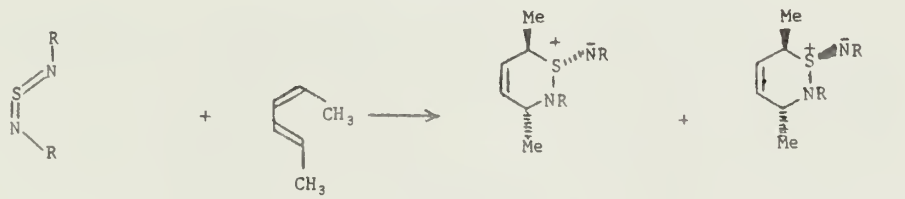
Figure 1.



11' **12'**

(E,E)-2,4 hexadiene afforded a 1:8 mixture of adducts **13** and **14** in 80% yield. Similarly, cylcoaddition of (E,Z)-2,4-hexadiene with **10a** and **10b** afforded a mixture of adducts **15** (~70%), **16** (few percent), and a 2.4:1 mixture of adducts **18** and **17** in 65% yield, respectively, as shown in Scheme V. The stereochemistry of each of the adducts was determined in the same manner as adducts **11** and **12**. Treatment of **12** and **14** with

Scheme V



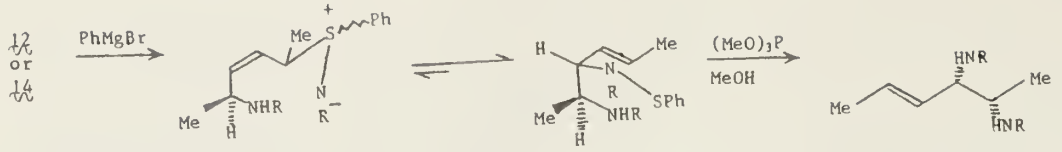
10a R = Ts
10b R = CO_2CH_3

15 R = Ts
17 R = CO_2CH_3

16 R = Ts
18 R = CO_2Me

phenylmagnesium bromide at -60°C, and then at reflux with trimethyl phosphate in methanol <u>in situ</u> gave a single (E)-<u>threo</u> vicinal sulfonamide **19** and E-threo vicinal carbamate **20** in excellent yield, respectively, as shown in Scheme VI. Similarly, adducts **15** and **17** gave

Scheme VI

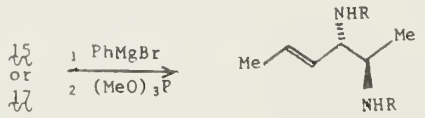


19 R = Ts, 20 R = CO_2CH_3

the (E)-erythro vicinal sulfonamide **21** and (E)-erythro vicinal carbamate **22** in excellent yield, respectively, as shown in Scheme VII. Surprisingly, the epimeric adducts **11**, **13**, and **18** did not react with phenylmagnesium bromide at temperature up to 0°C. This can be attributed to steric hindrance by the cis methyl group to the nucleophilic replacement at sulfur which was required for the ring opening step.

Treatment of these "unreactive" adducts with either phenyllithium or methyllithium at -60°C, followed by trimethyl phosphite gave the corresponding threo and erythro products, but the yields were low (from 38% to 51%). It was discovered that refluxing "unreactive" adducts **11**, **13** and **16**, **18** in benzene produced stable thiadiazolidines in quantitative

Scheme VII



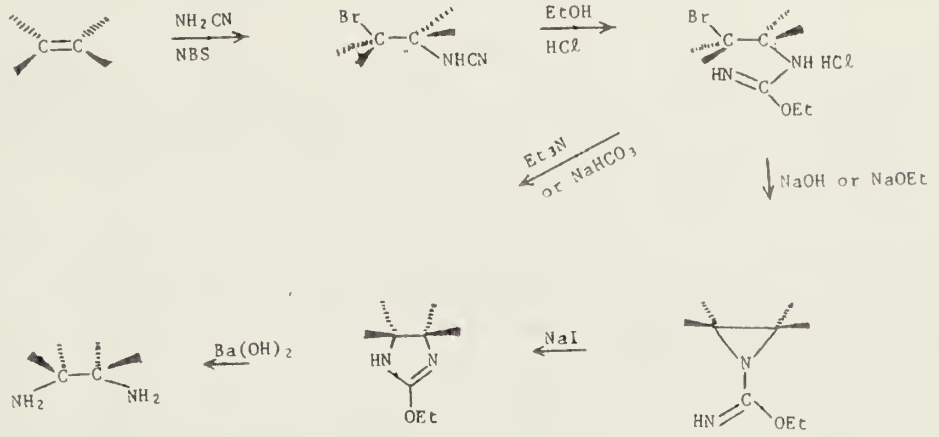
21 R = Ts
22 R = CO_2Me

yields. These products can be reduced by sodium borohydride to give the corresponding threo **19**, **20** and erythro **21**, **22** isomers in 70-90% yields. Interestingly, this later method was unsuccessful with "reactive" adducts, such as **14**. On heating **14** in toluene only extensive decomposition was observed. This methodology also can be applied to cyclic dienes. Bis(imine) **10b** was added to 1,3-cyclohexadiene, followed by several similar steps to give cis-vicinal carbamate in overall 62% yield.

Stereospecific Preparation of Vicinal Diamines from Olefins and Cyanamide.

Kohn and Jung[6] have recently reported new methodology for conversion of unactivated alkenes to nitrogen-unsubstituted diamines based on the formation of aziridines or imidazolines. The procedure is depicted in Scheme VIII. Alkenes can react with N-bromo-succinimide and cyanamide to give the corresponding alkyl cyanamide which can be converted to a protonated isourea salt under acidic conditions. Treatment of the protonated isourea salt with mild base produced the corresponding imidazolines stereospecifically. In the case of the cis-alkene series, better yields were obtained by treatment of the isourea salt with strong base to generate the aziridine which could be converted to the imidazoline

Scheme VIII

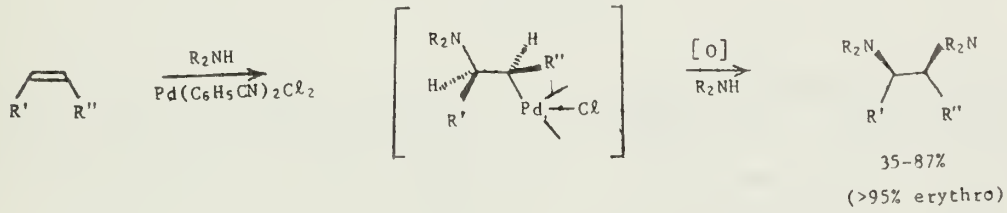


with sodium iodide. Both formation of aziridine and its conversion to imidazoline proceeded stereospecifically. Finally, basic or acidic hydrolysis of the imidazolines gave the desired diamines in 51% to 71% overall yield.

Transition Metal-Based 1,2-Diamination of Alkenes.

The use of transition metals to synthesize the vicinal diamines from alkenes has resulted in a few successful one-pot procedures. Backvall[11] reported that olefins can be stereospecifically transformed into vicinal diamines by the aminopalladation-oxidation sequence, depicted in Scheme IX. This method worked very well on terminal olefins

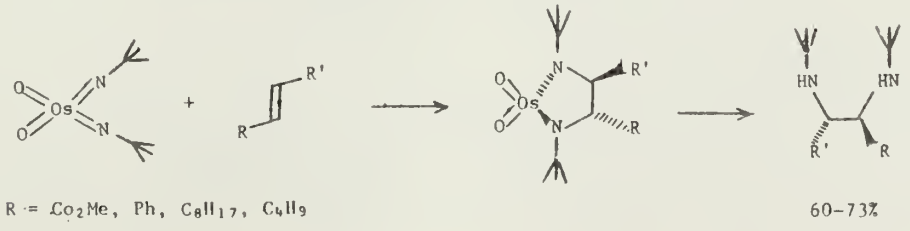
Scheme IX



(60-87%); however, with internal olefins the yields were low (e.g., 35% from 2-trans-octene).

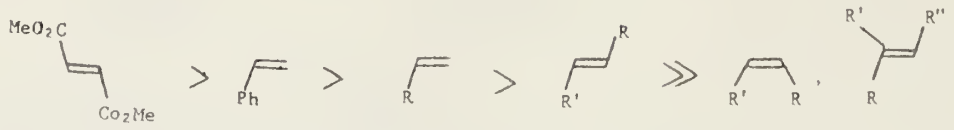
Another stereospecific vicinal diamination of olefins was reported by Sharpless et al.,[11] who employed diimido and triimido osmium (VIII) complexes which reacted with olefins to form osmium (VI) diimido complexes which gave diamines under reduction, as shown in Scheme X. Once again, cis olefins and heavily substituted olefins were less

Scheme X



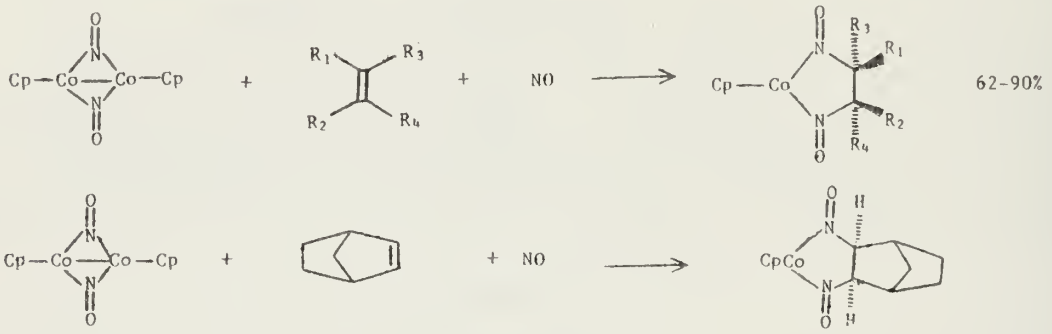
reactive, as shown in Figure 2. Both of the above methods suffered from the limitation of providing only N-alkylated secondary or tertiary amines.

Figure 2.



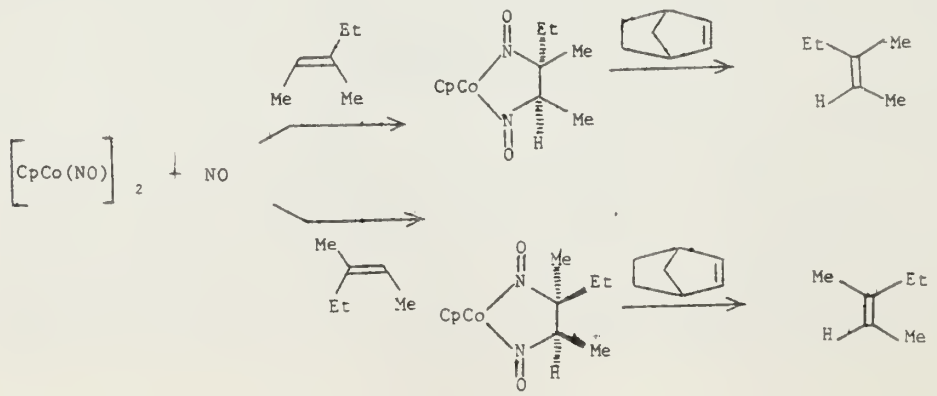
The first general method for the direct transformation of olefins into primary 1,2-diamines was reported recently by Bergman and co-workers.[5] This approach works satisfactorily for terminal, di(E,Z), tri and at least some tetrasubstituted alkenes. The olefins were allowed to react with nitric oxide and ($^5\eta$-cyclopentadienyl)nitrosyl cobalt dimer to produce cobalt 1,2-dinitrosoalkane complexes stereospecifically. The cobalt nitrosyl dimer reacted with norbornene in the presence of NO to form cis-exo complexes. The structure of the species was confirmed by

Scheme XI



X-ray diffraction[5d] (see Scheme XI). For acyclic olefins, the same stereospecificity was established by ^{1}H NMR spectroscopy and by olefin exchange [5a] (see Scheme XII). Finally, the cobalt dinitrosoalkanes could be converted to the desired vicinal diamines by hydride reduction in overall yields of 47-80%. Unfortunately, the hydride reduction produced stereoselectively, as the major product, diamines formed by syn addition of two NH_2 groups to the olefins. It has also been found that the stereoselectivity of the $LiAlH_4$ step and the diamine yield appeared to parallel the thermal stability of the correpsonding dinitrosoalkane complex.

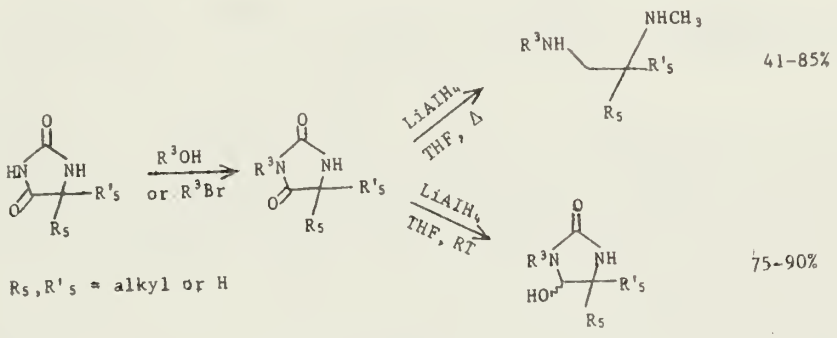
Scheme XII



Synthesis of Some Special Vicinal Diamines from Hydantoin.

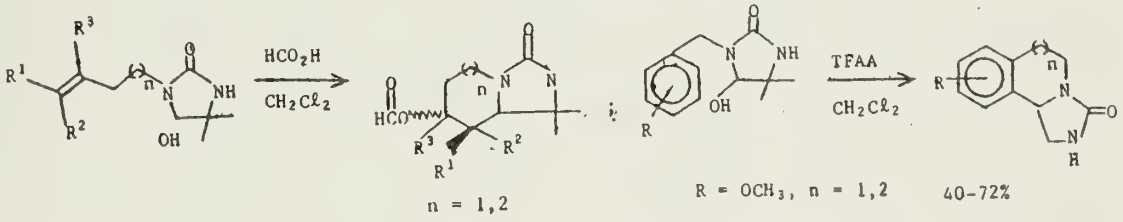
The synthesis of some special vicinal diamines from the readily available compound hydantoin and its derivatives was reported by Kohn and Liao[7a] who found that the nitrogen-3 of hydantoin would be alkylated with appropriate alcohols or bromides. The N-3-substituted hydantoins would be selectively reduced to 4-hydoxy-2-imidazolidinones and vicinal diamines by $LiAlH_4$ at different temperatures[7d], as shown in Scheme XIII. A variety of annelated 2-imidazolidinones were synthesized by intra-

Scheme XIII



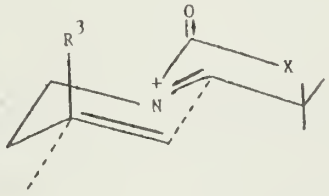
molecular imido-alkylation via N_3-alkenyl and N_3-aromatic substituted 4-hydroxy-2-imidazolidinones.[7b,c] In the case of carbon-5-disubstituted 4-hydroxy-2-imidazolidinones, these synthons underwent cyclization efficiently to yield six- and seven-membered ring adducts. In the former case the reaction proceeded with a high degree of stereospecificity in moderate yield,[7a] as shown in Scheme XIV. The stereoselective ring

Scheme XIV



closure was explained in terms of the Stock-Eschenmoser hypothesis in which the reaction proceeded through a chairlike transition state as depicted in Figure 3. In the case of carbon-5-unsubstituted- and mono-

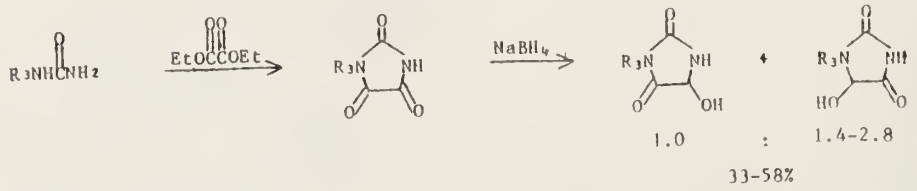
Figure 3.



substituted-4-hydoxy-2-imidazolidinones, the desired amido alkylation transformation did not occur but rather competitive dehydration yielded 2-imidazolones. Two modifications were discovered to circumvent this dehydration process.[7c] One involved the use of reactive allylsilanes. Thus, the placement of an allysilane unit in the N-3 side chair of

hydantoins should allow access to annelated 2-imidazolidinones independent of the substitution pattern at C-5. Another approach was to place a carbonyl group at C-5 to block the dehydration process. This approach was exemplified by reduction with $NaBH_4$ to the desired C-5 blocking compounds, of parabanic acid which had been prepared from the corresponding substituted ureas and diethyl oxalate, as shown in Scheme XV.

Scheme XV



After annelation the carbonyl blocking group can be removed by $LiAlH_4$ reduction at room temperature. All of these annelated imidazolidinones would be converted to a variety of vicinal diamines by either hydrolytic or reductive methods.

These newly developed methods have overcome some limitations of the classical ones. Most of the new approaches give moderate to excellent yields, are highly stereospecific, and start with readily accessible compounds.

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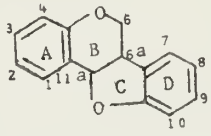
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BIOSYNTHESIS OF PTEROCARPAN PHYTOALEXINS

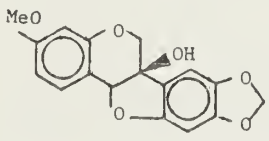
Reported by Terri L. Jakuboski March 25, 1985

Phytoalexins are low molecular weight antimicrobial agents whose formation is induced in the plant by infection with either living microorganisms or elicitors (products of microbial origin, heavy metal salts), or by stress treatment (cold, UV light).[1] The majority of the phytoalexins identified so far are produced by members of the Leguminosae (Fabaceae) and Solanaceae plant families and belong to a wide variety of natural products which include isoflavonoids, sesquiterpenes, polyacetylenes and dihydrophenanthrenes. Because of the potential of phytoalexins in plant disease resistance, understanding the biosynthetic pathways to these compounds is important in order to clarify defense mechanisms of the plants.

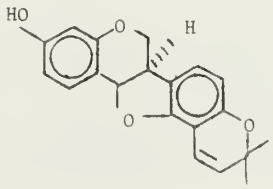
An important class of the isoflavonoid phytoalexins is the pterocarpan phytoalexins which have the basic skeleton shown below.



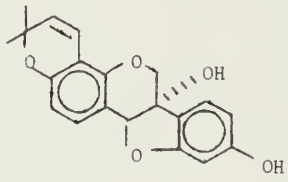
These phytoalexins are produced mainly by infected plants of the bean (Leguminosae) family. Compounds of this type include (+)-pisatin **1** isolated from pea tissue (pisum sativum),[2] (-)-phaseollin **2** isolated from French bean (phaseolus vulgaris)[3] and glyceollin I **3** isolated from soybean (glycine max).[4]



1



2

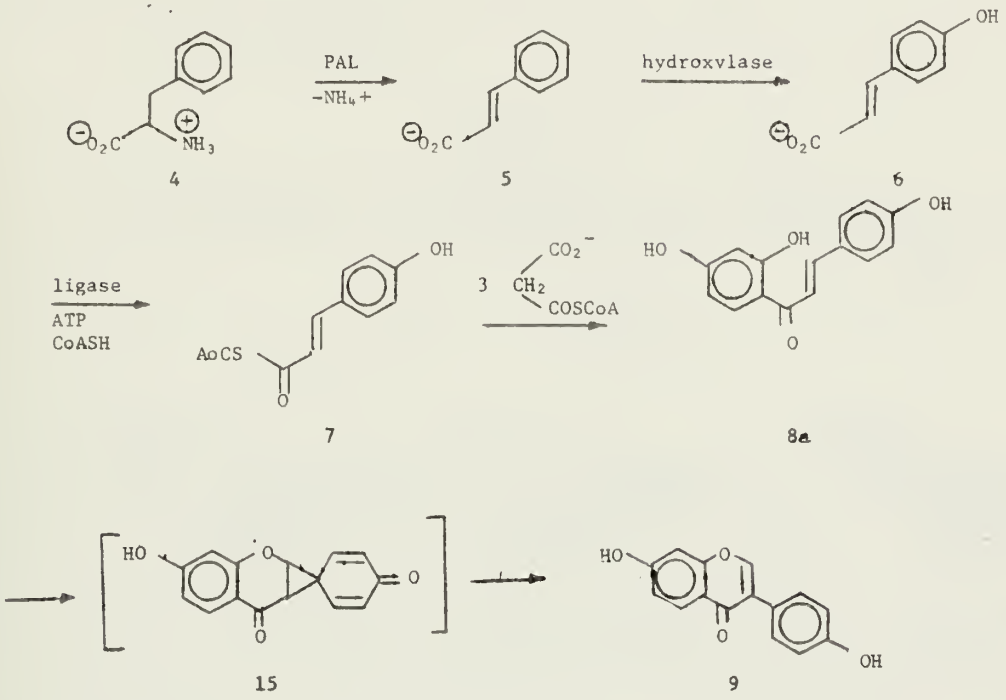


3

The metabolic pathway leading to the isoflavonoid skeleton involves the coenzyme A esters of 4-hydroxycinnamic acid (4-coumaric acid) and malonic acid (Scheme I).[5] The elimination of ammonia from L-phenylalanine **4** which is catalyzed by phenylalanine ammonia-lyase (PAL) gives cinnamic acid **5**. Hydroxylation to 4-hydroxycinnamic acid **6** and activation by ligase in the presence of ATP and coenzyme A gives the CoA ester **7**. The enzyme chalcone synthetase then catalyzes the

condensation reaction of 4-coumaroyl CoA **7** with three molecules of malonyl CoA to give the chalcone skeleton **8a**. Finally, the chalcone **8a** is converted to the isoflavone **9** possibly via the spirodienone **15**.

Scheme I

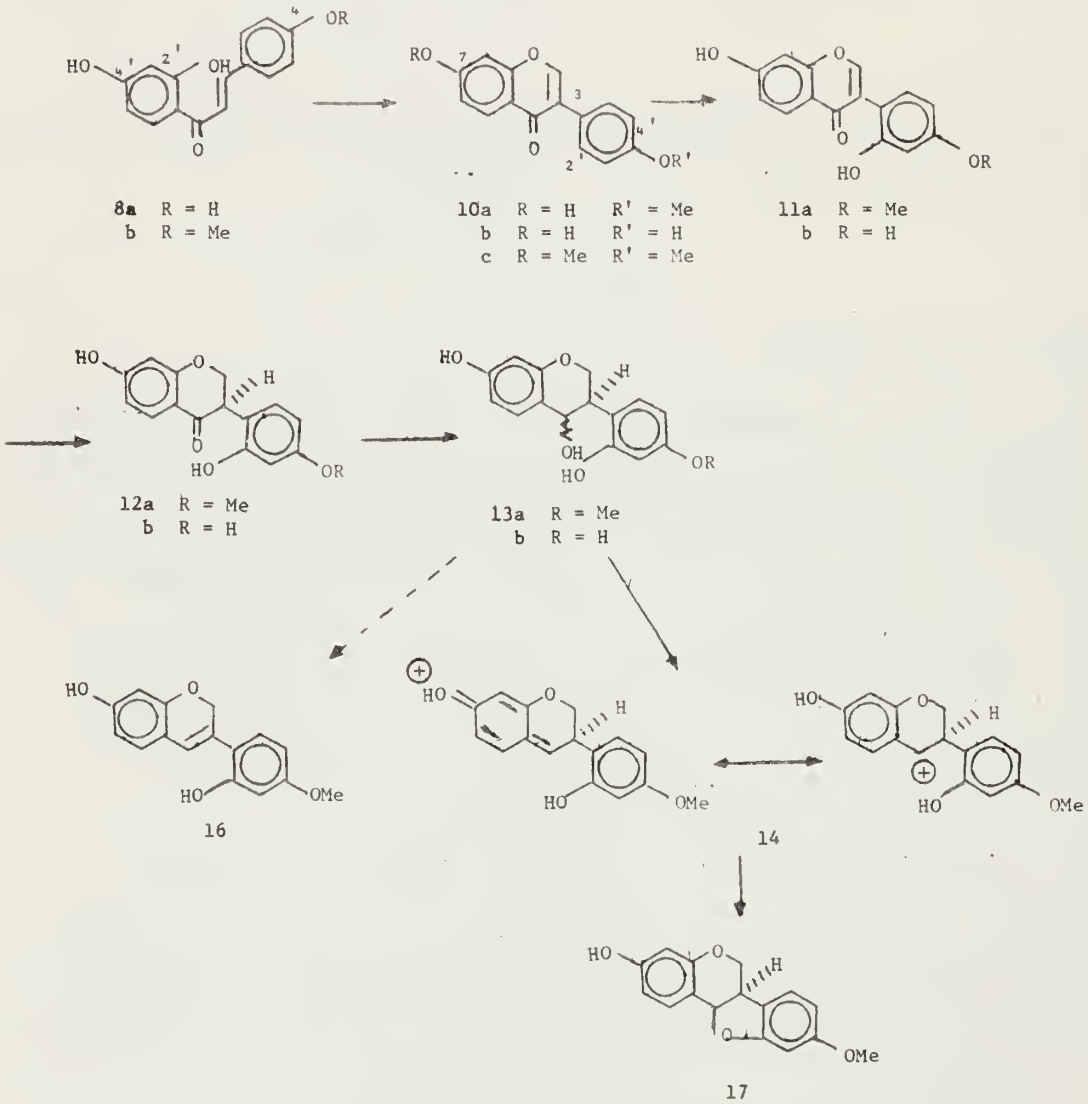


Non-prenylated pterocarpans

The most common of the isoflavonoid phytoalexins produced by leguminous plants upon treatment by biotic or abiotic agents is (-)-(6aR, 11aR)-dimethylhomopterocarpan or medicarpin **17**. Less frequently, a second pterocarpan (-)-(6aR,11aR)-maackiain **23a** is synthesized simultaneously with **17**. The biosynthesis of medicarpin **17** has been investigated by feeding experiments in chemically-treated seedlings of red clover (Trifolium pratense),[6] lucerne (medicago sativa)[7] and fenugreek (Trigonella foenum-gracium).[8] In all of these plants, the biosynthetic pathway of medicarpin **17** appears to be as follows (Scheme II). The 2',4',4-trihydroxychalcone **8a** is converted to formononetin **10a** possibly via the spirodienone **15**. Feeding experiments with $CuCl_2$-treated Trifolium pratense have shown that 2', 4'-dihydroxy-4-methoxychalcone **8b** and daidzein **10b** are inefficient precursors.[6,9,10] Thus offering evidence that methylation is an associated part of the mechanism for aryl migration in formononetin **10a** biosynthesis. Hydroxylation and two successive reductions follow to give **13a**. Using ^2H NMR spectroscopy, it has been determined that there is an overall trans addition of hydrogen to the double bond of **11a**.[8] The isoflavanol **13a** then cyclizes to yield the pterocarpan **17** with a mesomeric carbonium ion **14** being postulated as an intermediate.[7] The

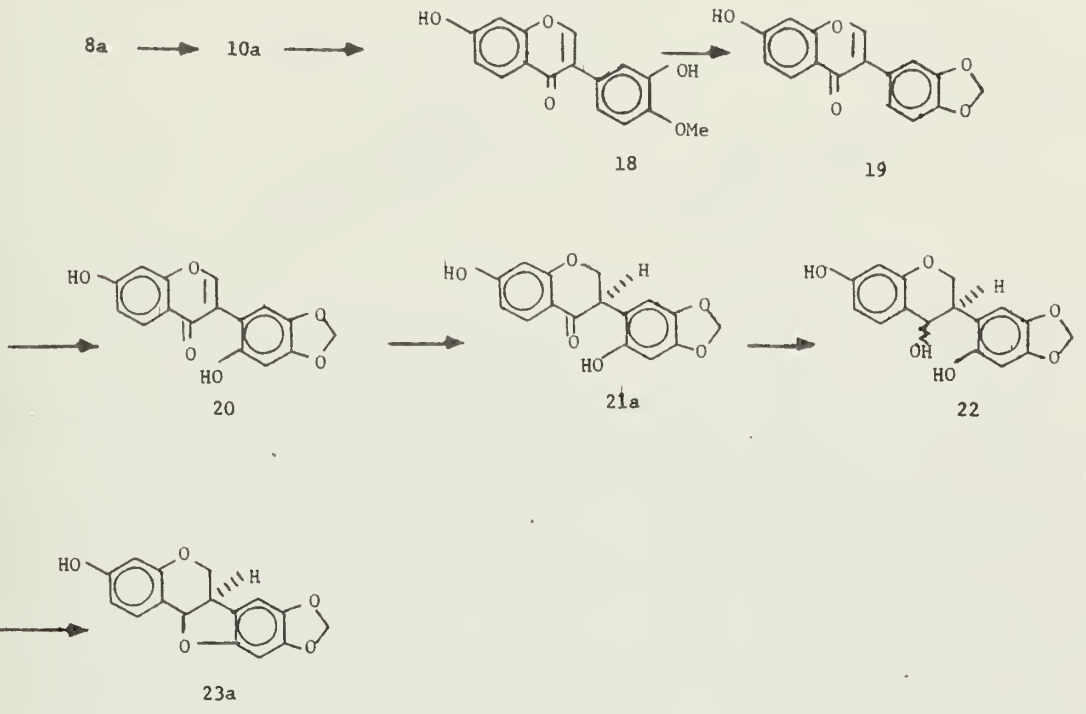
proposal of the carbonium ion as an intermediate in pterocarpan biosynthesis is chemically logical, but biologically, such a species would need to be stabilized, perhaps by being bound to an enzyme. A more attractive possibility from a biochemical viewpoint would be the isoflav-3-ene **16** derived by dehydration of the isoflavanol **13a**. The isoflav-3-enes are chemically very reactive but have been excluded as biosynthetic precursors of the lucerne phytoalexins,[7] pea phytoalexins[11,17] or as intermediates in the pterocarpan-2'-hydroxyisoflavan interconversion.[12] They do, however, play an important role in the biosynthesis of 3-aryl coumarins and coumestans.[13]

Scheme II



The pathway to maackiain **23a** in red clover, however, branches from that of medicarpin **17** probably at formononetin **10a** because of poor incorporation of **12a** and **17**.[6b] Further feeding experiments in Cu^{+2}-treated red clover seedlings have demonstrated that ^{14}C- labeled formononetin **10a** and isoflavones **18**, **19** and **20** are readily converted to maackiain **23a**.[14] These compounds represent a logical biosynthetic sequence for elaboration of the substitution pattern as shown in Scheme III.

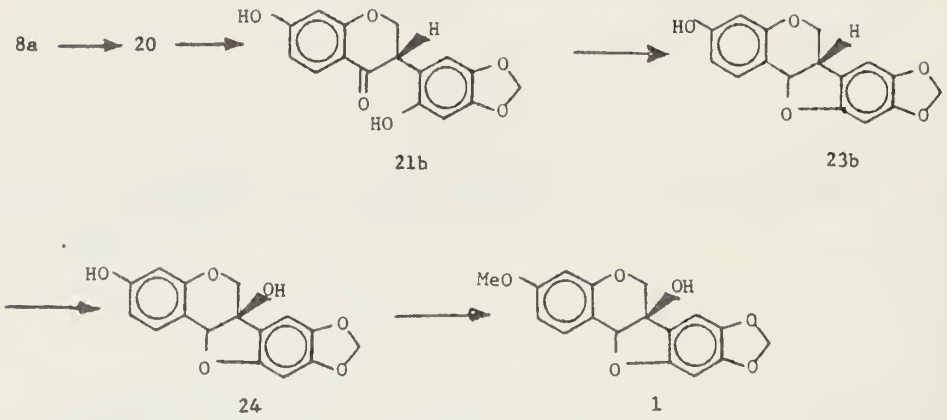
Scheme III



(+)-(6aR,11aR)-Pisatin **1** is a 6a-hydroxypterocarpan produced by pea tissue (pisum sativum) on fungal infection or abiotic treatments. It is unusual amongst pterocarpan phytoalexins in having the opposite absolute configuration to other reported examples. Hadwiger briefly investigated its biosynthesis in cupric chloride-treated pea pods and found good incorporations of phenylalanine, cinnamic acid, acetate and methionine.[15] Tyrosine, however, proved to be a poor precursor. The mode of incorporation of acetate which involves a specific folding of the polyketide chain and reduction of one carbonyl function prior to aromatization was established by Stoessl and Stothers using ^{13}C NMR.[16] Dewick has proposed the biosynthetic pathway from the trihydroxychalcone **8a** to (+)-pisatin **1** as shown in Scheme IV.[17] The sequence to the isoflavone **20** is the same as for (-)-maackiain **23a**, but at that point there is a cis addition of hydrogen to the double bond to yield **21b**.

Subsequent reduction and cyclization to (+)-(6aS,11aS)-maackiain **23b** followed by 6a-hydroxylation and O-methylation yields (+)-(6aR,11aR)-pisatin **1**.

Scheme IV

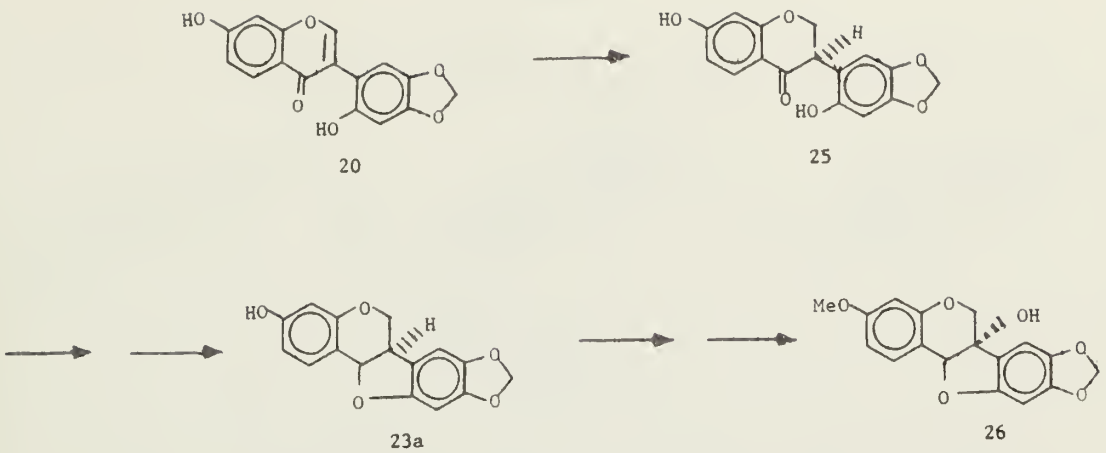


Comparative feeding experiments in cupric chloride treated pea pods and seedlings have shown good incorporation into (+)-pisatin **1** of radiolabeled precursors of maackiain **23** and maackiain itself.[17] There was poor incorporation, however, of methyl formononetin **10c** suggesting that the 3-O-methyl group of pisatin is introduced later in the pathway and of daidzein **10b** which again has been interpreted in terms of methylation of the 4-hydroxy group during the aryl migration process. Although daidzein **10b** may be enzymatically methylated to formononetin **10a**, the incorporation data suggest that this process may not account for the major portion of formononetin **10a** production.

The stereochemistry of the 6a-hydroxylation of (+)-maackiain **23b** to (+)-pisatin **1** has been determined to proceed with retention of configuration at C-6a.[18] Dewick has shown in experiments with enantiomeric precursors that incorporation of (+)-[^{3}H]-maackiain was preferred to (-)-[^{14}C]-maackiain in (+)-pisatin **1**.[11] This seems reasonable because any inversion process would necessitate the additional inversion at C-11a since pterocarpans have a cis-fused ring system.

(-)-Pisatin **26** has also been isolated as a minor metabolite of abnormal configuration produced by pisum sativum. Its biosynthetic pathway is similar to (+)-pisatin **1** except that the isoflavone reduction proceeds via an overall trans addition of hydrogen to give (-)-maackiain **23a** and subsequent 6a-hydroxylation with retention of configuration to give (-)-pisatin **26** (Scheme V).[18]

Scheme V

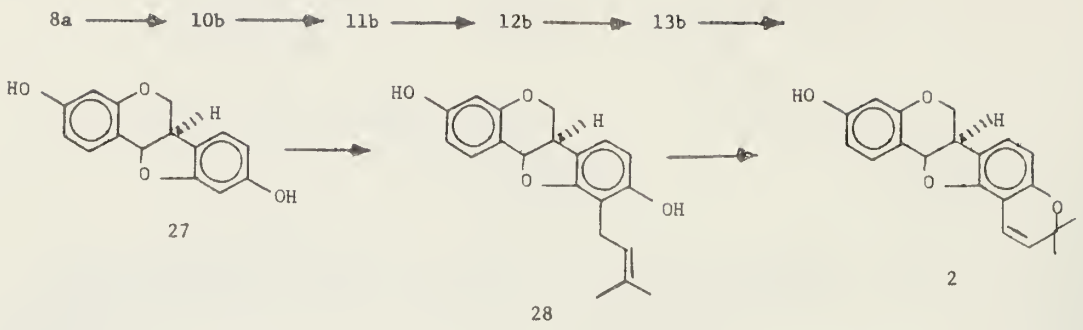


Prenylated pterocarpans

(-)-Phaseollin **2** is a prenylated phytoalexin isolated from infected tissues of French bean (Phaseolus vulgaris). A biosynthetic pathway has been suggested by Dewick and is outlined in Scheme VI.[21] Hess and co-workers first demonstrated the incorporation of phenylalanine, cinnamate, acetate and daidzein **10b** in $CuCl_2$-treated bean pods.[19] Mevalonic acid though was poorly utilized. The incorporation of sodium [1,2-$^{13}C_2$] acetate into phaseollin **2** has been studied using ^{13}C-NMR[20] and it was found there was incorporation of intact acetate units into the aromatic A ring and involved a specific folding of the polyketide chain and reduction of the oxygen function before formation of the aromatic ring as with pisatin **1**.[16]

Feeding studies with radiolabeled precursors in $CuCl_2$-treated French bean seedlings have shown that 2',4',4-trihydroxychalcone **8a**, daidzein **10b**, 7,2',4'-trihydroxyisoflavone **11b**, 3,9-dihydroxypterocarpan **27** and phaseollidin **28** are all readily converted to the pterocarpan which is in agreement with the proposed pathway.[21] The ready incorporation of all precursors tested suggests that the pterocarpan skeleton is synthesized before any prenylation occurs. This parallels data obtained in the rotenoid amorphigenin biosynthesis where prenylation is also delayed until the rotenoid skeleton has been constructed.[9] Ring closure to phaseollin **2** may involve an intermediate epoxide by analogy with postulated pathways for other cyclized hemiterpenoids, but there is no direct evidence yet to suppport this.[22]

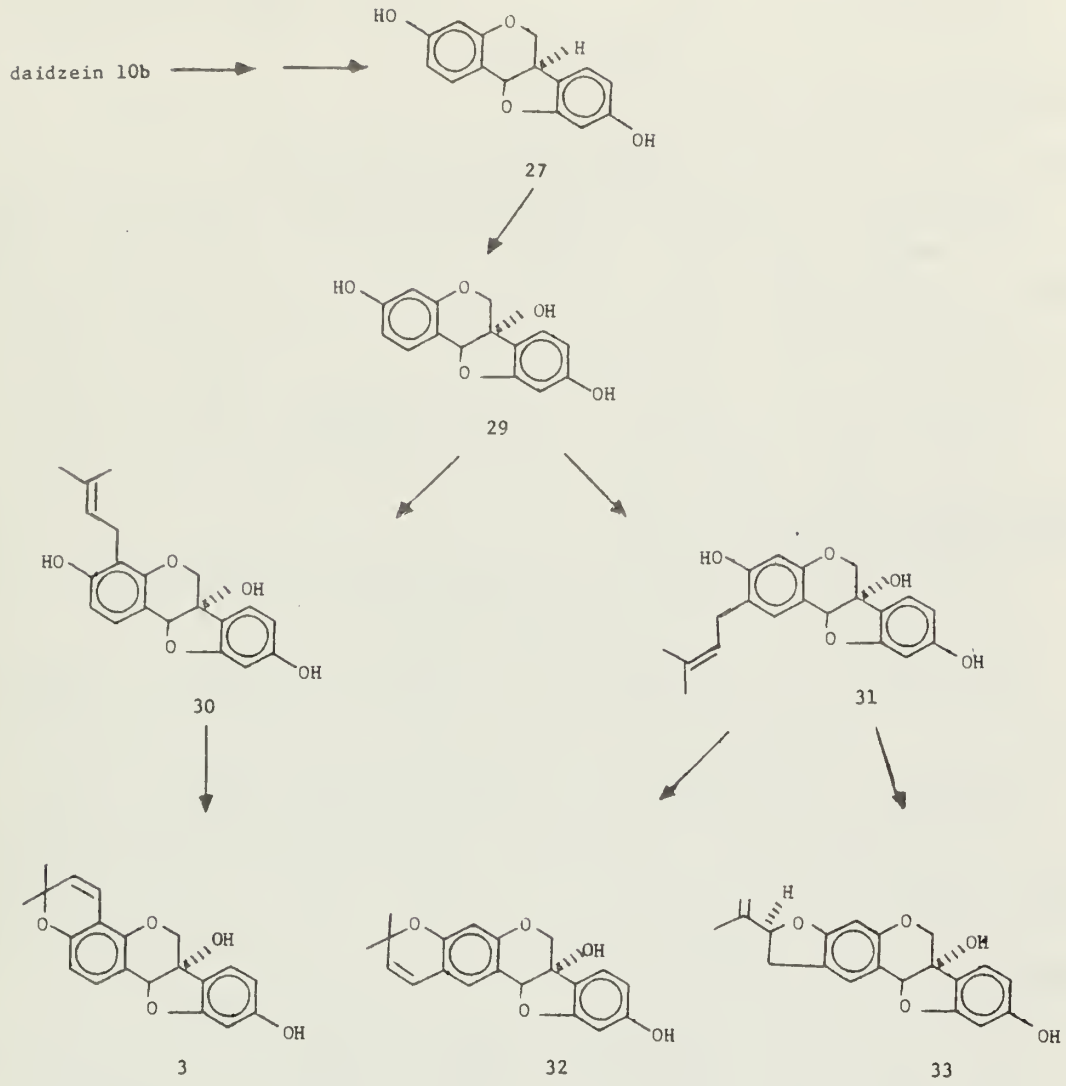
Scheme VI



Several other important prenylated pterocarpans are the isomers of glyceollin which are synthesized as phytoalexins by soybean (glycine max.) tissues. The biosynthetic pathway proposed is similar to the one proposed for phaseollin biosynthesis (Scheme VII).[23] Instead of the occurrence of prenylation after ring closure to **27**, a stereospecific 6a-hydroxylation takes place to give **29**. The 6a-hydroxylase has been found in elicitor-induced soybean cultures by Grisebach.[24] The prenylated derivatives, glyceollins I **3**, II **32**, III **33**, are then derived from glycinol **29** via glyceollidin I **30** or II **31** and would be produced by cyclization of the 3-hydroxyl group onto the dimethylallyl moiety, perhaps via an intermediate epoxide as suggested with phaseollin **2**.

To define the pathway, Dewick has conducted a series of feeding experiments in $CuCl_2$-treated soybean seedlings and pods.[23] The results indicate that ^{14}C-labeled phenylalanine, daidzein **10b**, 7,2',4'-trihydroxyisoflavone **11b**, 3,9-dihydroxypterocarpan **27** and glycinol **29** are efficient precursors of each of the 3 glyceollins, though there was a variation in proportions of the individual isomers in the seeds and pods. Presumably, the site of dimethylallylation of glycinol is controlled in some way in the induced plant tissue and this may depend on the tissue or method of induction. These results suggest that the 6a-hydroxypterocarpan skeleton is synthesized before prenylation occurs which is in agreement with the results obtained from phaseollin[21] and the rotenoid amorphigenin biosynthesis.[9] Also, the isolation of dimethylallyl tranferase enzyme from glucan elicitor-treated soybean cotyledons catalyzing the synthesis of glyceollidins I **3** and II **32** from glycinol **29** and dimethyllallyl pyrophosphate support this hypothesis.[25]

Scheme VII



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PALLADIUM CATALYZED CROSSED-COUPLING REACTIONS OF ORGANOTIN REAGENTS AND ELECTROPHILES

Reported by Gordon W. Selling March 28, 1985

The reaction of an organometallic reagent with a suitable electrophile is a general method for creating a new carbon-carbon bond. It has been reported that if the reactant is a transition metal complex, the new bond can be created both regio and stereospecifically.[1] However, there are a number of functional groups that are not compatible with many typical organometallic reagents, and many less reactive organometallic reagents, either are difficult to synthesize or cannot contain certain functional groups or both.[1,2] Organotin reagents appear to be unusual in that they are able to tolerate a wide variety of functional groups and still can be used in carbon-carbon bond formation. For example, esters, nitriles and even aldehydes are stable to organotin reagents.[3,4] The organotin reagent itself can also bear a variety of functional groups such as esters, alcohols and ethers.[5,6] It has been found that using palladium catalysis, organotin reagents can be coupled with a variety of electrophiles under mild conditions to give the direct crossed-coupled product, or crossed-coupled ketone if allowed to react in the presence of carbon monoxide.[1,5] Of the four organic groups bound to tin, simple alkyls were transferred slowest.[1,5,7] A second transfer of an organic group from tin was found to be approximately 100 times slower.[5]

Coupling of Organotin Reagents with Aryl or Benzyl Halides. The palladium-catalyzed crossed-coupling reaction of organolithium or Grignard reagents with organic halides has been investigated (equation 1), and was found to give large amounts of homocoupling products rather than the desired crossed-coupling products.[8]

$$RX + ML_n \longrightarrow RML_nX + R'M' \longrightarrow RR' + M'X + ML_n \qquad (1)$$

R = Aryl, benzyl X = halide M' = Li, MgX
M = transition metal L = ligand

When methyllithium or methylmagnesium bromide was added to benzyl chloride with various palladium catalysts, the major product was bibenzyl with very little crossed-coupling product, ethylbenzene, formed.[8] When instead of organolithium or Grignard reagents, organotin reagents were allowed to react with aryl or benzyl halides under an inert atmosphere with palladium

catalysis, the crossed-coupled product was obtained almost exclusively.[8] The results in Table 1 show that good yields are obtained when benzylchlorobis(triphenylphosphine)palladium (II) (**1**) is used as catalyst.[8a]

Table 1

Reaction of Organotin Reagents with Organic Halides

$$R_3SnR' + R''X \xrightarrow[HMPA]{3\ mole\%\ PhCH_2Pd(PPh_3)_2Cl\ (1)} R'R'' + R_3SnX$$

R''X	R_3SnR'	R'R'' (% yield)	R_3SnX (% yield)
$PhCH_2Br$	Me_4Sn	$PhCH_2CH_3$ (82)	Me_3SnBr (85)
$PhCH_2Br$	$(n\text{-}Bu)_3SnCH{=}CH_2$	$PhCH_2CH{=}CH_2$ (100)	$(n\text{-}Bu)_3SnBr$ (95)
PhBr	Ph_4Sn	PhPh (78)	not determined
$4\text{-}CH_3COC_6H_4Br$	Me_4Sn	$4\text{-}MeCOC_6H_4CH_3$ (95)	Me_3SnBr (98)

It was also determined that the reaction gave the best yields of crossed-coupled product when hexamethylphosphoramide (HMPA), a highly polar aprotic solvent, was used.[8] The most productive air stable catalysts were **1** and benzylbromobis-(triphenylphosphine)palladium (II) (**2**).[8] When the palladium-catalyzed reaction of organotin reagents with benzyl

$PhCH_2Pd(PPh_3)_2Br$

2

or aryl halides were carried out in the presence of oxygen, reaction rates went up.[8] With 1.7 equivalents of oxygen the reaction of tetramethyltin, benzyl bromide and 2 mole % of **1** gave 11.3% of ethylbenzene in two hours. With 40.1 equivalents of oxygen and 204 equivalents of oxygen the yields of ethylbenzene were 38.8 and 81.2% respectively under the same reaction conditions.

If the reaction was performed under a carbon monoxide atmosphere with 0.2 mol % of benzyliodobis(triphenylphosphine)-palladium (II), the crossed coupled ketone can be obtained (equation 2).[10] The yield of crossed-coupled ketone ranged from 62-85%.

$$RX + R'_4Sn \xrightarrow{PhCH_2Pd(PPh_3)_2I} \underset{\displaystyle O}{\overset{\displaystyle \|}{RCR'}} + R'_3SnX \qquad (2)$$

R = Aryl, Benzyl R' = Methyl, n-Butyl, Phenyl
X = Cl, Br, I

When stoichiometric amounts of **2** and tetramethyltin were allowed to react under the same reaction conditions that had been employed with catalytic amounts of **2**, very little ethylbenzene resulted (equation 3).[11] When the reaction was

$$Me_4Sn + \underset{\displaystyle \mathbf{2}}{PhCH_2Pd(PPh_3)_2Br} \xrightarrow[HMPA]{65°C} N.R. \qquad (3)$$

repeated at 25°C, the major products were trans-methylbromobis-(triphenylphosphine)palladium (II) and benzyltrimethyltin (equation 4).[11] This is interesting since two metal-carbon bonds but no metal-halogen bonds were broken.

$$Me_4Sn + \underset{\displaystyle \mathbf{2}}{PhCH_2Pd(PPh_3)_2Br} \xrightarrow[HMPA]{25°C} \underline{trans}\text{-}MePd(PPh_3)Br + PhCH_2SnMe_3 \qquad (4)$$

When trans-methylbromobis(triphenylphosphine)palladium (II) and benzyltrimethyltin were allowed to react at 65°C in HMPA, once again very little ethylbenzene resulted. However, as seen in Table 2, when p-nitrobenzyl bromide (2 equivalents) was added to the reaction of **1** or **2** and tetramethyltin yields went up (equation 5).[11] And if inverse addition was used, where **1** or **2** is added to a solution of the organotin reagent and p-nitrobenzyl bromide, yields went up dramatically.[11]

$$PhCH_2Pd(PPh_3)_2X + Me_4Sn + p\text{-}NO_2PhCH_2Br \longrightarrow PhCH_2CH_3 + p\text{-}NO_2PhCH_2Pd(PPh_3)_2X + Me_3SnX \qquad (5)$$

1 X = Cl
2 X = Br

Table 2

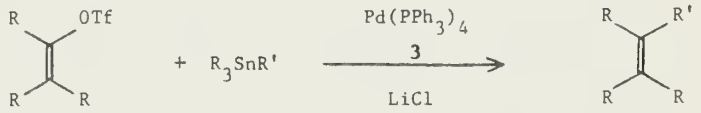
Reaction of Benzylpalladium Complexes with Tetramethyltin

complex	additive	$PhCH_2CH_3$ % yield
1	--	1.8
2	--	0.0
1	$p\text{-}NO_2PhCH_2Br$	30.7[a]
1	$p\text{-}NO_2PhCH_2Br$ (inverse addition)	81.3[a]
2	$p\text{-}NO_2PhCH_2Br$ (inverse addition)	87.2[a]
$p\text{-}NO_2PhCH_2Pd(PPh_3)_2Cl$	$PhCH_2Br$[b]	100[a]

[a]No p-nitroethylbenzene was found. [b]Two equivalents

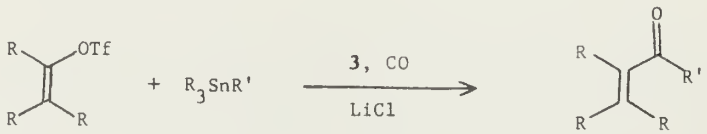
Coupling of Organotin Reagents with Allyl and Vinyl Electrophiles. The palladium-catalyzed reaction of allyl or vinyl electrophiles, with organotin reagents produced the crossed-coupled product in generally good yields.[1,5,6,21-25] In the presence of carbon monoxide, the crossed-coupled ketone can be obtained.[5,6,12]

Vinyl triflates and vinyl iodides both gave good yields of crossed-coupled product when allowed to react with organotin reagents using palladium catalysis.[12-14] As seen in Table 3, the yields ranged from 78 to 100%, for the reaction of vinyl triflates and organotin reagents catalyzed by 2 mole % of tetrakis(triphenylphosphine)palladium (0) (**3**) (equation 6).[14]



(6)

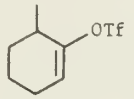
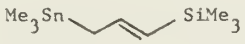
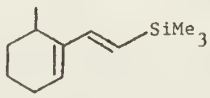
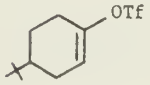
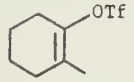
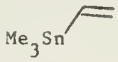
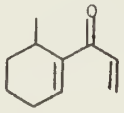
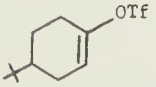
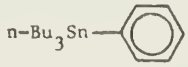
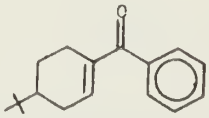
As shown in Table 3, if carbon monoxide was present and 3 mol % of **3**, carbon monoxide insertion resulted, and ketones were obtained in good yields (equation 7).[12] For both of these reactions, 6 and 7 to occur, two equivalents of lithium chloride was necessary.[12,14]



(7)

Table 3

Palladium Catalyzed Crossed-Coupling of Organotin Reagents with Vinyl Triflates

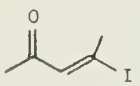
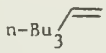
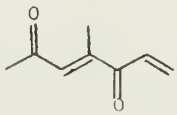
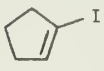
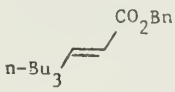
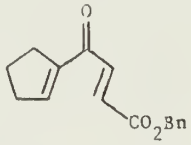
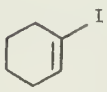
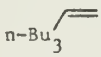
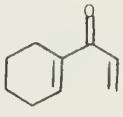
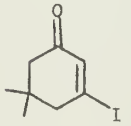
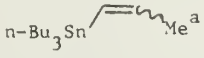
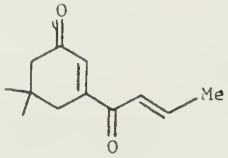
Vinyl Triflate	Organotin	P(psi)CU	Product (% yield)
		--	 (100)
	$n\text{-}Bu_3SnH$	--	 (78)
		15	 (78)
		15	 (93)[a]

[a]One equivalent of $ZnCl_2$ was used instead of two equivalents of LiCl.

Vinyl iodides react with organotin reagents with 1-2 mol % of **1** or dichlorobis(triphenylphosphine)palladium (II) in a carbon monoxide atmosphere, to give the crossed-coupled ketone in fair to good yields as seen in Table 4.[13]

Table 4

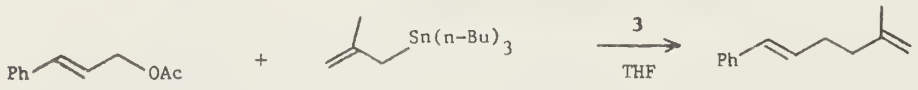
Carbonylative Crossed-Coupling of Vinyl Iodides with Organotin Reagents Catalyzed by **1** or Dichlorobis(triphenylphosphine)palladium (II)

Vinyl Iodide	Organotin	Product (% yield)
		 (50)
		 (40)
		 (93)
		 (71)

[a]Z/E ratio was 6.

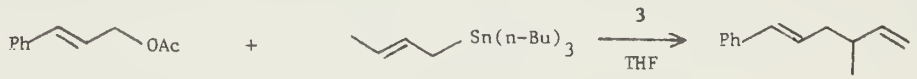
The advantage of the vinyl triflate methodology to produce the crossed-coupled ketone, is the ease of forming the regiospecific vinyl triflate using known enolate chemistry.[12]

Allyl acetates and allyl halides have been reported to undergo crossed-coupling reactions with organotin reagents using palladium catalysis.[1,5,15,16] Unlike allyl chlorides, allyl acetates do not give regiospecific products in all cases.[15] For example, when α-methallyl-tri-n-butyltin was allowed to react with cinnamyl acetate with 4 mol % of **3**, the desired regiospecific crossed-coupled product, with respect to the allyl acetate, was obtained in 69% yield (equation 7).[15]

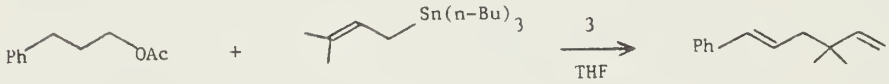


(7)

However, crotyl-tri-n-butyltin (equation 8) or prenyl-tri-n-butyltin (equation 9) when treated with cinnamyl acetate and 4 mol % of **3**, gave only products of allyl inversion in the allyltin reagent.[15]

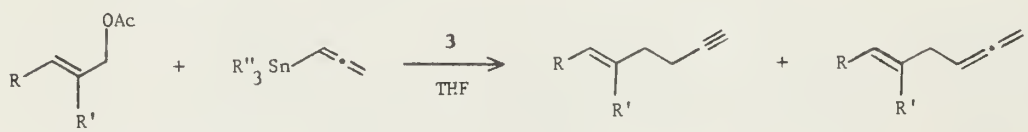


(8)



(9)

Allylic acetates also reacted with allenyl organotin reagents with 5 mol % of **3**, to produce 1,5-enyne systems and allenes in combined yields of 23 to 93% (equation 10).[16] The isomeric ratio between the alkyne and the allene ranged from 50:50 to 100:0.[16]

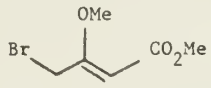
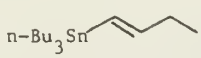
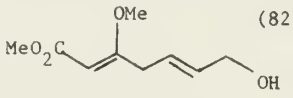
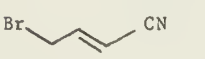
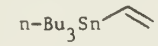
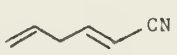
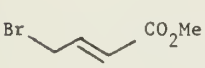
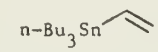
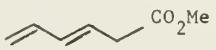
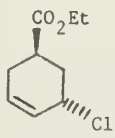
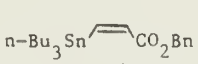
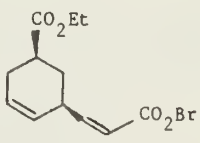
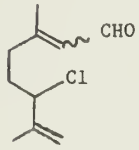
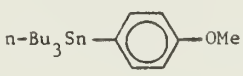
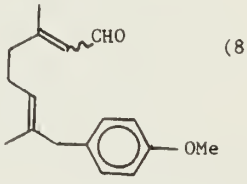


(10)

The palladium-catalyzed reaction of allyl halides and organotin reagents produced the crossed-coupled product in yields ranging from 56-94%.[1,5] The mild reaction conditions and the use of an organotin reagent allows a variety of functional groups to be present on the components, as shown in Table 5.

Table 5

Palladium-Catalyzed Coupling of Allyl Halides with Organotin Reagents

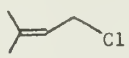
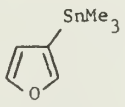
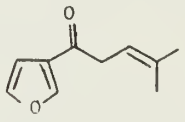
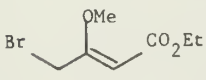
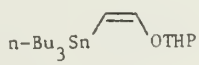
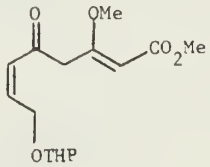
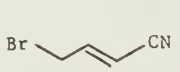
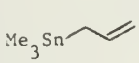
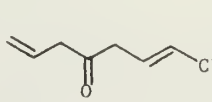
Allyl Halide	Organotin	catalyst	Product (% yield)
		3 mole % $Pd(dba)_2$[a] +2 PPh_3	 (82)
		1 mole % 1	 (65)
		1 mole % $(CH_3CN)_2PdCl_2$ + .5 PPh_3	 (87)
		3 mol % $Pd(dba)_2$ +2 PPh_3	 (80)
		3 mol % $Pd(dba)_2$ +2 PPh_3	 (87)

[a] bis(dibenzylideneacetone)palladium (0)

When these reactions were carried out in the presence of carbon monoxide, the crossed-coupled ketone resulted from insertion of carbon monoxide.[5,6] As seen in Table 6, yields vary widely.

Table 6

Carbonylative Crossed-Coupling of Allyl Halides with Organotin Reagents

Allyl Halide	Organotin	Catalyst	Product (% yield)
		$Pd(dba)_2$ + 2 PPh_3	 (75)
		$Pd(dba)_2$ + 2 PPh_3	 (74)
		$(CH_3CN)_2PdCl_2$ + 2 PPh_3	 (16)

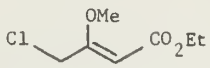
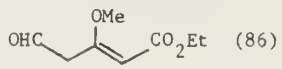
Aldehydes could also be obtained from the reaction of tri-n-butyltin hydride and a vinyl, allyl or aryl halide in the presence of carbon monoxide and 3.5 to 4 mol % of **3** (equation 11).[17] As seen in Table 7, product yields ranged from fair to excellent.

$$RX + n\text{-}Bu_3SnH \xrightarrow[CO]{3} R\text{—}CHO \qquad (11)$$

R = vinyl, allyl or aryl
X = Cl, I

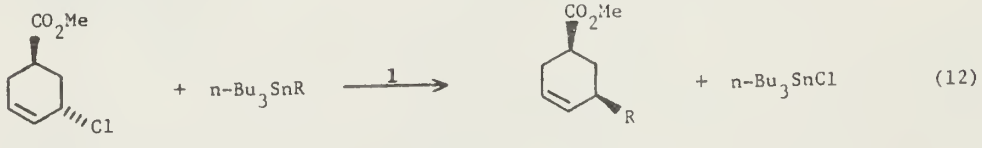
Table 7

Reaction of Vinyl, Allyl or Aryl Halides with Tri-n-butyltin Hydride in Carbon Monoxide Atmosphere Catalyzed by **3**

entry	Organic Halide	Product (% yield)
1	p-MePhI	p-MePhCHO (100)
2	p-NO_2PhI	p-NO_2PhCHO (38)
3	o-$HOCH_2$PhI	o-$HOCH_2$PhCHO (55)
4		 (86)

Note that in entry 3, the aldehyde was obtained despite a hydroxyl group present which could have added to the transition metal complex.

Stereochemistry. The stereochemistry of the palladium-catalyzed reaction of allyl chlorides with organotin reagents was studied by allowing cis and trans-3-chloro-5-carbomethoxycyclohexene (**4**) to react with phenyl-tri-n-butyltin or vinyl-tri-n-butyltin in the presence of .5 mol % of **1** (equation 12).[1,5]



(12)

trans- **4** cis- **5**

R = Ph, $CH{=}CH_2$

The reaction was found to proceed with allylic carbon inversion to produce cis-**5**. When the reaction was not allowed to go to completion, both the theoretical amount of organotin reagent and

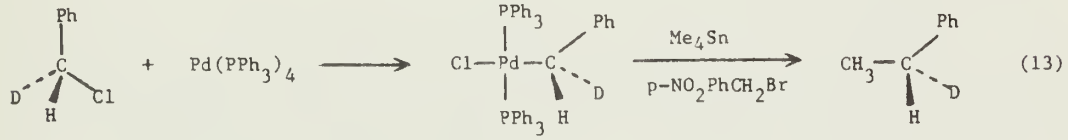
unepimerized **4** were recovered.[5] When a mix of cis- and trans-**4** were allowed to react, the ratio of cis- and trans-**5** depended only on the original ratio of cis and trans-**4** as seen in Table 8.[5]

Table 8

Palladium-Catalyzed Coupling of Organotin Reagents with cis- and trans- **4**

$n\text{-}Bu_3R$ R	**4** cis/trans	**5** cis/trans
Ph	27/73	75/25
$CH{=}CH_2$	27/73	71/29

The stereochemistry of the reaction of (R)-(-)-benzyl-α-d-chloride (**6**) with **3** to produce (S)-chloro-(α-deuteriobenzyl)-bis(Triphenylphosphine)palladium (II) (**7**) (equation 13) followed by reaction with tetramethyltin and p-nitrobenzyl bromide gave a 92.1% yield of (R)-(-)-α-deuterioethylbenzene (**8**) (30.3 ± 2.8% ee).[11] Therefore the

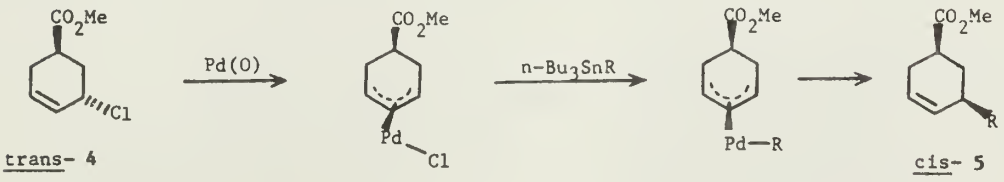


(R) - **6** **3** (S) - **7** (R) - **8** (13)

conversion of **6** to **8** occurs with a stereospecificity 38.9 ± 3.7%.[11] It has also been determined that oxidative addition of **6** to **3** occurs with 74% net inversion of configuration.[11] Thus, the conversion of **7** to **8** occurs with 52.6 ± 5% net retention of configuration.[11]

Mechanism of Palladium-Catalyzed and Stoichiometric Palladium Crossed-Coupling Reactions. Based on the stereochemical results obtained from equation 12, the mechanism detailed in Scheme 1 was proposed.[5] The Palladium (0) was

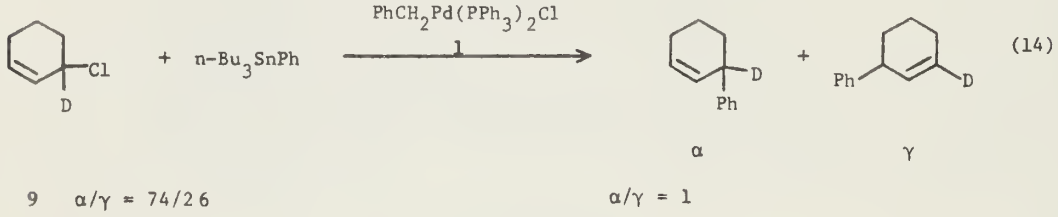
Scheme 1



trans- **4** cis- **5**

presumed to come from transmetalation of **1** by the organotin, followed by reductive elimination. Oxidative addition of **4** to palladium (0) has been shown to occur with inversion to give the allyl-palladium (II) complex.[5] At this point the complex has the same stereochemistry as the product. Therefore the next two steps, transmetalation and reductive elimination, must either both occur with inversion of configuration or both occur with retention of configuration. It has been shown that reductive elimination occurs with retention of configuration,[8,11] therefore the transmetalation step probably occurs with retention of configuration also.[5]

The nature of the allyl-palladium (II) complex has been studied using deuterium labeling in the reaction of 3-deuterio-3-chlorocyclohexene (74% α-D, 26% γ-D) (**9**) with phenyl-tri-n-butyltin with 1 mol % of **1** (equation 14).[5]



(14)

9 α/γ = 74/26 α/γ = 1

3-Phenylcyclohexene with deuterium distribution essentially equal (50:50 γ-D:α-D ± 2%), as determined by ^{2}H NMR, between the α and γ positions was obtained. This would suggest that both positions are equivalent, and the allyl-palladium (II) complex is either a rapidly equilibrating σ-complex or a symmetric π-allyl complex.[5] When the reaction was not allowed to go to completion, the recovered starting material had the same deuterium distribution as did the original starting material **9**.

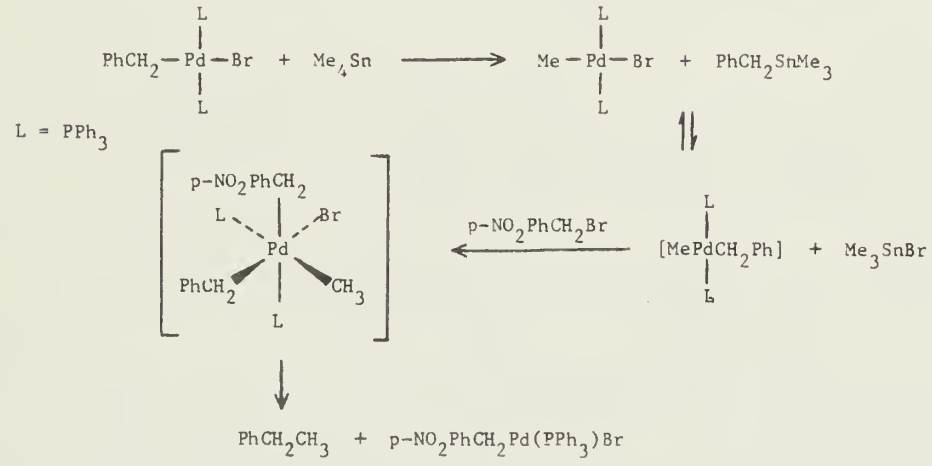
As shown earlier, reaction of **2**, an organotin reagent and p-nitrobenzyl bromide gave crossed-coupled product in good yield. When stoichiometric amounts of p-nitrobenzylchlorobis-(triphenylphosphine)palladium (II) (**10**), tetramethyltin and benzyl bromide reacted, the crossed-coupled product obtained was ethylbenzene, no p-nitroethylbenzene was found (equation 15).[11]

$$p\text{-}NO_2PhCH_2Pd(PPh_3)_2Cl + Me_4Sn + PhCH_2Br \longrightarrow PhCH_2CH_3 + Me_3SnCl + p\text{-}NO_2PhCH_2Pd(PPh_3)Br \quad (15)$$

$$Me_4Sn + PhCH_2Pd(PPh_3)_2Br \xrightarrow{25°C} \underline{trans}\text{-}MePd(PPh_3)_2Br + PhCH_2SnMe_3 \quad (4)$$

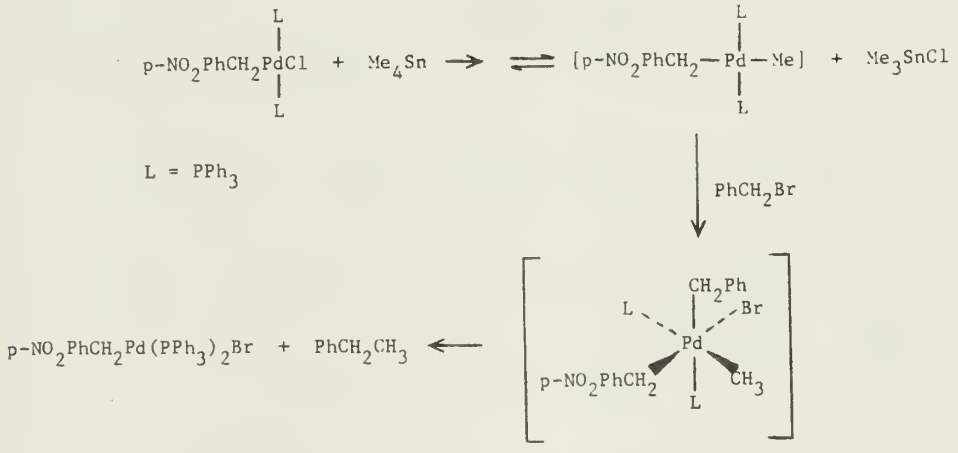
With these results, and the results from equation 4, the mechanism shown in Scheme 2 was proposed for the reaction of 2, tetramethyltin and p-nitrobenzyl bromide.[11]

Scheme 2



The absence of p-nitroethylbenzene can be explained by a comparison of the p-nitrobenzyl-palladium (II) bond strength and the benzyl-palladium (II) bond strength.[11] The benzyl-palladium (II) bond is weaker and would preferentially undergo reductive elimination. The reaction described in equation 15 supports this mechanism, since the benzyl bromide must add to the palladium (II) complex in order to have the methyl in the required cis position (Scheme 3).[11]

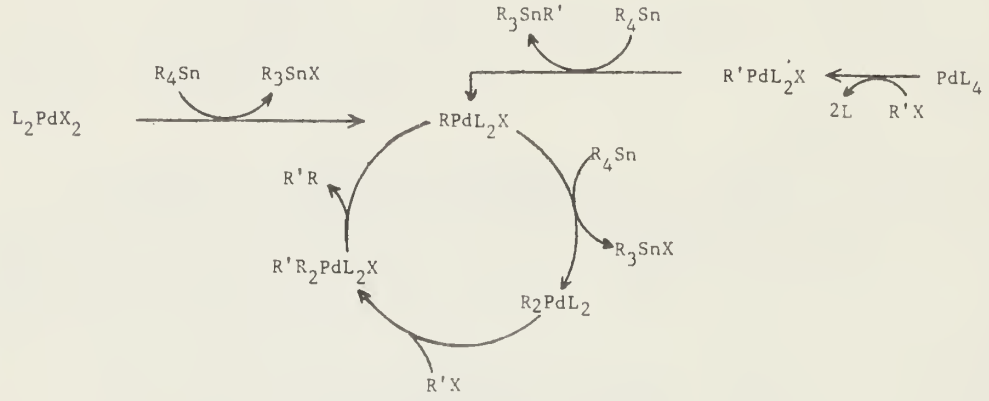
Scheme 3



A free radical mechanism, which could explain some of the observed results, was rendered unlikely by the high stereospecificity observed for the reaction, which is inconsistent with a random free radical mechanism.[11]

Based on the information obtained from the stoichiometric palladium reactions, the catalytic cycle shown in Scheme 4 was proposed for the palladium-catalyzed reaction of organic halides with organotin reagents.[8]

Scheme 4



It can be seen then that palladium-catalyzed crossed-coupling involving organotin reagents, is a very mild and efficient route to carbon-carbon bond formation. Some additional electrophiles which can undergo coupling with transition metal complexes which have not been discussed here: acid chlorides to produce ketones[18] or aldehydes,[19] haloketones to produce cyclic ethers,[20] and diazonium salts to produce ketones.[21] Consequently, the palladium-catalyzed crossed-coupling reaction of an organotin reagent and an electrophile is a very general route to carbon-carbon bond formation.

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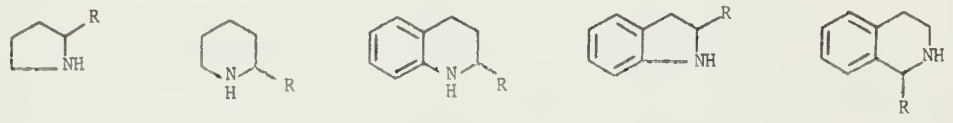
CHROMATOGRAPHIC RESOLUTION OF HETEROCYCLIC AMIDES: MECHANISM AND APPLICATIONS

Reported by George Mahler April 8, 1985

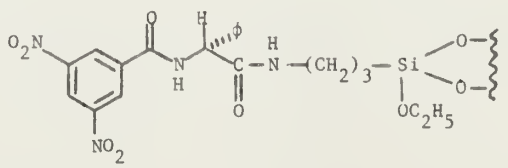
As the focus of organic chemistry has turned squarely toward the total control of stereochemistry in synthetic procedures, the answers to the fundamental questions of stereochemistry have become urgent: first, how is a pure, single enantiomer of a compound obtained; second, how is enantiomeric purity determined; and, third, how is absolute configuration determined. Though a methodology still in its infancy, the direct liquid chromatographic resolution of enantiomers on chiral stationary phases[1] (CSPs) has shown the promise of providing answers to these three questions simultaneously.

For a chiral stationary phase to exhibit enantioselectivity, the association of the analyte enantiomers with the CSP must yield two diasteriomeric adsorbates of differing stability.[2] Though efficient separations can be obtained from diasteriomeric adsorbates of small energy differences, the greatest utility of CSP's stems from an ability to predict absolute configuration of a given enantiomer based on elution order. The specification of discrete adsorbates as being the lower in energy of two possible is not trivial and requires an understanding of the interactions involved in chiral recognition. Though *a priori* based on the elution order of compounds of known absolute configuration, a chiral recognition mechanism for a given analyte type/CSP system must consider analyte and CSP conformation as well as configuration.

A variety of heterocyclic amines, 1-5, derivatized as their 1-naphthamides, have been found to resolve on CSP 1.[3]



1 2 3 4 5



CSP 1

As reported[4], the enantiomers of primary and simple secondary amines may also be separated on CSP 1. However, unlike the amides of primary amines, secondary and heterocyclic amine amides exist as a mixture of diasteriomeric rotamers and their distribution need not be statistical.[5] Indeed, examination of molecular models revealed that for amides of amines 1-5, predicted elution order depends on the rotamer involved in chiral recognition. Dynamic nuclear magnetic resonance, however, has revealed that the E rotamer - except for the 1-naphthamides of indoline - is the most heavily populated.[6]

Recently, this technique has been used by Meyers[7] who has developed a method for the asymmetric alkylation of α-aza carbanions. Sense of elution from CSP 1 of the 1-naphthamides of heterocyclic amines agrees with the expected sense of asymmetric alkylation. Conveniently, both sense and degree of asymmetric induction may be quantified simultaneously.

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NONLINEAR OPTICAL PROPERTIES OF ORGANIC COMPOUNDS

Reported by Robert C. Hall April 11, 1985

The potential applications of materials exhibiting nonlinear optical properties have generated considerable interest in the past few years. Future progress in communication fields and information processing may depend on optical as well as electronic devices. Most of the research in nonlinear optics up to the present has been done in research labs such as those at IBM, Xerox, Kodak, Bell Laboratories, and British Telecom. The largest optical nonlinearities yet observed occur in organic crystals and polymer films. An understanding of the origin and nature of nonlinear optical phenomena will help organic chemists in preparing better nonlinear optical materials.

Nonlinear optics involves the interaction of electromagnetic fields in a medium (such as a crystalline solid) to produce new fields with propagation characteristics differing from the original incident fields. When an electromagnetic field interacts with a collection of molecules, the molecules are polarized by the field. These molecules then act as oscillating dipoles which generate new electromagnetic radiation. The polarization P induced in a single molecule by an electric field is described by Equation (1), where E is an

$$P = \alpha E + \beta E^2 + \gamma E^3 + \ldots \qquad (1)$$

electric field, and α, β, γ are the first, second, and third order molecular hyperpolarizability coefficients. A similar expression for a medium consisting of an array of molecules is given by Equation (2), where $\chi^{(1)}$, $\chi^{(2)}$, and $\chi^{(3)}$ are the first, second, and third order susceptibilities.

$$P = \chi^{(1)}E + \chi^{(2)}E^2 + \chi^{(3)}E^3 + \ldots \qquad (2)$$

At weak field strengths only the first terms in equations (1) and (2) are observed. This results in linear polarization and is observed as refraction of the incident light. When an intense field, such as that produced by laser beam, interacts with a medium, the second, third, and higher order nonlinear terms of equations (1) and (2) may affect the polarization, resulting in nonlinear optical effects.

The best known nonlinear optical effect is second harmonic generation (SHG), the production of light with frequency 2ω ($\omega+\omega$) from incident light of frequency ω. Other second order effects include the linear electro-optic (Pockels) effect, where an electromagnetic field $E(\omega)$ interacts with a DC field $E(0)$ ($\omega+0$), and optical rectification, where a DC voltage is created between electrodes placed on the surface of a crystal when a laser beam passes through the crystal ($\omega-\omega$). Third order nonlinear optical effects (resulting from γ and $\chi^{(3)}$), such as third harmonic generation ($\omega+\omega+\omega$), are much weaker than second order effects like SHG. Higher order effects are observed at very large field strengths, but are too weak to be of much use.

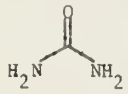
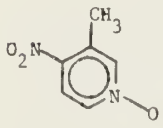
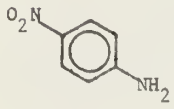
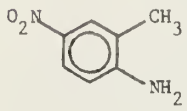
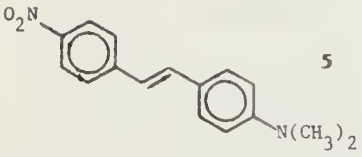
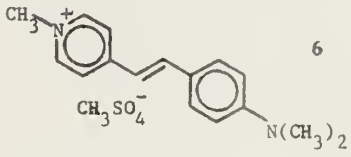
The coefficients α, β, and γ in equation (1) are tensor quantities and thus are symmetry dependent. The odd order coefficients α and γ are nonzero for all molecules, but the even order β is zero for molecules possessing a center of symmetry. Similarly, $\chi^{(2)}$ is equal to zero in centrosymmetric media. Second order nonlinear optical effects are only observed in media possessing a polar direction. This requires that the molecules making up the media have permanent dipole moments and that these dipoles are not cancelled out by statistical averaging or centrosymmetric crystallization (i.e., the unit volumes of the media must have permanent dipoles oriented in the same direction).

Generation of nonlinear optical effects occur most efficiently when phase-matching conditions are present in the nonlinear media. Many crystals exist that have certain directions along which both the incident and induced radiation are phase-matched (propagate with identical speeds). Phase matching minimizes destructive interference that reduces nonlinear optical efficiency.

The value of β for organic molecules can be determined experimentally by electric field-induced second harmonic generation (EFISH).[1] In this method a strong DC field is applied to a solution of molecules in order to remove the orientational averaging of molecular dipoles. Laser light is then pulsed through the solution to cause second harmonic generation, from which the value of β can be calculated. Some β values, powder SHG efficiencies, and absorption cuttoffs for organic molecules are given in Table I.[2]

Table I

Some Organic Nonlinear Materials

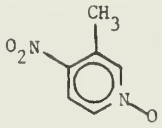
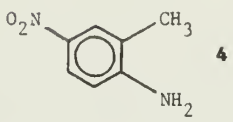
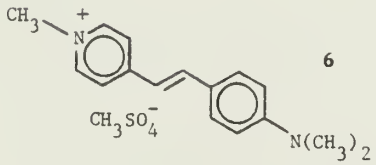
Structure		β(x 10^{-30} esu)	SHG Powder efficiency (x area)	absorption cuttoff (nm)
	1	0.45	1.0	200
	2	5	13	410
	3	35	0	470
	4	42	22	480
	5	450	0	580
	6	--	250	588

All of the molecules in Table I are both conjugated and polar. The general trend is that increasing conjugation length and increasing polarity lead to larger β coefficients and higher possible SHG efficiency. Increase in the magnitude of β is accompanied by an increasing red shift in the absorption edge of the molecules, which reduces the frequency range in which the molecules are useful as nonlinear optical media (media must be optically transparent to both incident and induced radiation). This "efficiency-transparency trade-off" can be seen by comparing SHG efficiencies and absorption cuttoffs in Table I. Note also that 4-nitroaniline 3 and trans-4-dimethylamino-4'-nitrostilbene 5 have zero powder SHG efficiencies even though they possess large β coefficients. This is due to centrosymmetric crystallization.

Organic materials with π-electron systems offer some important advantages over inorganic substances (like lithium niobate) as nonlinear optical media. Highly polarizable delocalized π-electron systems are the origin of the large optical nonlinearities in many organic crystals. The polarizability of inorganic substances depends more on larger less polarizable ions which allow less optical nonlinearity. Organic materials can respond to optical pulses on a shorter timescale than inorganics, and organic media generally have higher damage thresholds to laser irradiation. Table II shows some $\chi^{(2)}$ values for organic and inorganic materials.

Table II

Some Organic and Inorganic Materials

Compound	$\chi^{(2)}$ (esu)
KH_2PO_4	3×10^{-9}
$LiNbO_3$	1.5×10^{-8}
 **2**	3×10^{-8}
GaAs	1×10^{-7}
 **4**	7×10^{-7}
InSb	2×10^{-6}
 **6**	9×10^{-6}

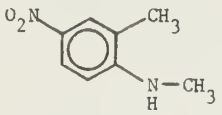
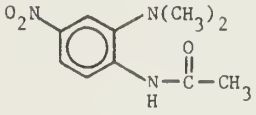
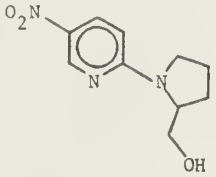
Preparation of organic materials for generation of practical nonlinear optical effects would require large molecular hyperpolarizabilities, noncentrosymmetric crystallization or alignment of the molecular units, and growth of large enough crystals or polymer samples for useful

applications. Molecules designed for second order nonlinear materials have so far been based largely on donor and acceptor substituted benzenes,[3] pyridines,[4] and stilbenes[5] which are both highly polar and conjugated.

Of the known crystal structures of organic compounds, about 70% involve crystallization of the molecules in centrosymmetric space groups[6] which results in the cancelling out of the molecular β coefficients and zero second order optical nonlinearity. One way of overcoming this statistical setback is by incorporating chiral centers into the molecules, thus preventing crystallization in centrosymmetric space groups. Twieg and Jain[2] believe that intermolecular hydrogen bonding in the crystalline state of the molecules shown in Table III is responsible for favorable alignment of the molecules in a noncentrosymmetric structure, causing some of the largest SHG efficiencies yet observed.

Table III

Some Highly Efficient Organic Nonlinear Optical Materials

Structure		SHG Powder efficiency (x area)
	**7**	80
	**8**	115
	**9**	160

causing alignment of the dopant molecules in the polymer. Efficient second harmonic generation in the doped polymer after cooling and removal of the field indicated that the dye molecules maintained their field-induced orientation.[7]

Large $\chi^{(2)}$ and $\chi^{(3)}$ susceptibilities have been found in single crystals and films of polydiacetylenes. Noncentrosymmetrically substituted diacetylene monomers can form large crystals which can be polymerized thermally or photochemically to form very long conjugated systems with large nonlinear optical efficiencies.[8,9]

The most serious obstacle to the application of organic compounds in nonlinear optics has been the growth of large enough crystals, but progress in crystal growth is constantly being made. The much larger degree of optical nonlinearity shown by organic over inorganic media makes the future application of organic compounds in nonlinear optics very promising.

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1,8-DIAZAFLUORENYLIDENE: A PROBE OF STRUCTURE AND REACTIVITY FOR AROMATIC CARBENES

Reported by Yu-zhuo Li April 15, 1985

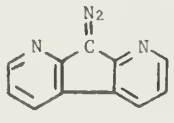
The effect of structure on the energy difference between the two lowest energy electronic states of carbenes, singlet and triplet, have been intensively approached by both experimentalists and theoreticians.[1] One objective of these studies is to establish a useful link connecting the structure of a carbene with its chemical properties. It is believed that the chemical properties of these intermediates are mainly controlled by their singlet-triplet energy gaps.

Several types of structural effects such as bond angle and p-π interaction have been studied in various carbene systems. Comparisons of diphenylmethylene,[2] fluorenylidene,[3] 9-mesityl-9-boraanthracene,[4] dibenzocycloheptadienelidene, and dihydrosilaanthracenylidene[5] show that the different chemical properties for these carbenes are due in part to the bond angle change. The bond angle affects the energy of singlet and triplet states differently.

Substituents affect diphenylcarbene and fluorenylidene. These groups change the energy gaps and sometimes reverse the ordering of the electronic states.[6] This shows that p-π interactions play an important role in the control of the properties of carbenes, too.

It is important to understand the σ-σ interaction effect and 1,8-diazafluorenylidene is a test of this type of effect on the energy gap between the singlet and the triplet states and their chemical properties. The two non-bonding orbitals of the diaza nitrogens can interact with the σ orbital of the carbene center to form an allylic-like system (Scheme I).

Scheme I



DADAF



DAFl

The products of reactions of DAF1 in several solvents indicate that, in contrast to the parent system, fluorenylidene, 1,8-diazafluorenylidene reacts with trapping reagents more rapidly than the establishment of the singlet-triplet equilibrium. A explanation for this is that the allyl-like system raises the energy of the σ-orbital of the carbene center and makes the p^2 singlet energetically possible.

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THE EXTENSION OF FORCE FIELD CALCULATIONS TO INCLUDE AMIDES AND SOME RECENT APPLICATIONS

Reported by Linda T. Pilla April 25, 1985

With an increasing availability of computer time, computational techniques for determining molecular structure (ab initio, semi-empirical and empirical force field calculations) are used to support observed data and to provide information on existing as well as nonexistent compounds. Since the amount of computational time necessary for ab initio and semi-empirical calculations is approximately proportional to the number of orbitals raised to the 4th and 2nd power respectively,[1a] their applications are limited to relatively small or medium sized molecules. The force field method, also known as the Westheimer method or molecular mechanics, in which computational time is proportional to the number of atoms squared,[1a] is often faster and more practical than other computational methods.

Force field calculations attempt to reproduce specific properties of a large number of related compounds from existing data for simpler molecules. The method applies the Born-Oppenheimer approximation which states that nuclei and electrons move independently and may be considered separately. Force field calculations consider the nuclei of molecules directly and consider electrons indirectly. Through a series of equations defining the properties of connected nuclei, molecular mechanics attempts to duplicate and predict an experimental outcome.

Equations

Force fields can be divided into two categories, valence and Urey-Bradley force fields. They differ mainly in the physical meaning of some constants, but the general equations are similar.[1] The following discussion will summarize information for a number of valence force fields which have been developed. Molecular mechanics considers the energy differences between a hypothetical "ideal" situation and the molecular conformation of interest.[1] For hydrocarbons, the energy parameters describing the total energy of a system (E_t) are the energy of bond stretching (E_s), bond angle bending (E_b), bond rotation (E_w) and nonbonded interactions (E_{nb}) (Eq. 1).[1] Cross terms describing the relation of bond stretching and bond angle deformation may also be included.

$$E_t = E_s + E_b + E_w + E_{nb} + \ldots \qquad (1)$$

In the first approximation, the nuclei of molecules are considered to be held together by elastic forces. Deviation from an "ideal" or "natural" bond length is considered to follow Hooke's law. After summation over all bonds, an estimation for bond stretching (E_s) will take the form shown in equation (2).[1] k_s is the force

$$E_s = \Sigma \frac{ks}{2} (\ell - \ell o)^2 \qquad (2)$$

constant for the specific bond type, ℓ_o is the "ideal" or "natural" bond length, and ℓ is the bond length in the species of interest. Constants k_s and ℓ_o are determined from spectroscopic data of small molecules such as ethane and propane.

Energy of bond bending (E_b) is considered to follow Hooke's law also, (Eq. 3)[1] where k_b and θ_o are constants determined from data

$$E_b = \Sigma \frac{k_b}{2} (\theta - \theta o)^2 \qquad (3)$$

of small molecules and θ is the experimental bond angle. Applying these equations to various molecules assumes the transferability of force constants between molecules of related structure. Hooke's law has proven adequate for small deviations from the "ideal", however, large deformations require higher level approximations and the use of Morse potentials.[1]

Torsional energy, or the energy for rotation about a bond (E_w), is commonly written as a Fourier series (Eq. 4), where V_1, V_2, V_3... are force constants

$$E_\omega = \Sigma [\frac{V_1}{2} (1 + \cos \omega) + \frac{V_2}{2} (1 - \cos 2\omega) + \frac{V_3}{2} (1 + \cos 3\omega) + \ldots] \qquad (4)$$

determined from rotational barriers of small molecules, and ω is the dihedral angle.[1]

The energy of nonbonded or Van der Waals interactions (E_{nb}) is usually accounted for in one of three ways: a Lennard-Jones potential, Hill function, or Buckingham potential. A Lennard-Jones potential (Eq. 5) has two possible forms. In the first form n equals 9 and in the second n equals 12. The value is chosen which gives the best fit of the data.[2] A and B are constants and r is the

$$E_{nb} = \Sigma \frac{A}{r^n} - \frac{B}{r^6} \qquad (5)$$

internuclear distance. An exponential form may also be used to define this energy curve such as the Hill function (Eq. 6)[1a] or Buckingham potential (Eq. 7).[1b] c_1, c_2 and c_3 are constants

$$E_{nb} = \Sigma\varepsilon[-c_1(\frac{r^*}{r})^6 + c_2 \exp(-c_3 \frac{r}{r^*})] \quad (6)$$

$$E_{nb} = \Sigma A' \exp(\frac{B'}{r}) + \frac{C'}{r^6} \quad (7)$$

taken to be universal, ε is an energy parameter used to describe the depth of the potential energy well, r is the interatomic distance, r* is the sum of Van der Waals radii and A', B' and C' are constants. The assumptions made in these equations are that the interactions may be summed over pairs of atoms and that interactions are the same no matter what is between the atoms. With these assumptions force field calculations have been successfully applied to unstrained hydrocarbons[1,3] and have been adjusted for strained hydrocarbons.[1a]

The extension of force field calculations to include heteroatoms, amides specifically, required adding constants for the equations discussed and including terms for electrostatic interactions and hydrogen bonds (Eq. 8[4,5,6] and 9[2,4b,5,6]). q_i and q_j are the

$$E_{el} = \Sigma c\frac{q_i q_j}{Dr_{ij}} \quad (8)$$

partial charges on nuclei i and j respectively,[7] r_{ij} is the distance between atoms, D is the dielectric constant and c is a constant to convert units. A''_{Hx} and B''_{Hx} are coefficients for

$$E_{hb} = \Sigma^{A''_{HX}/r_{ij}^{12}} - {}^{B''_{HX}/r_{ij}^{10}} \quad (9)$$

combinations of hydrogen bond donors and acceptors. Similar electrostatic, Van der Waals and hydrogen bonding terms may also be included to determine solvent effects.[5]

From the application of Coulomb's law[9] to account for spatially oriented dipole-dipole interactions, the following alternate description of electrostatic interactions (Eq. 10)[8] has recently been

$$E_{dd} = \Sigma[\vec{\mu}_1 \cdot \vec{\mu}_2 - 3(\vec{\mu}_1 \cdot \hat{n})(\vec{\mu}_2 \cdot \hat{n})]r_{ij}^{-3} \quad (10)$$

used. E_{dd} is the energy of dipole-dipole interactions, $\vec{\mu}_1$ and $\vec{\mu}_2$ are vector dipole moments associated with bonds 1 and 2, $\hat{n}$ is the unit vector in the direction of the position vector between 1 and 2. Force fields have also taken into account terms for interactions between atoms bonded to common atoms and the out-of-plane deformation angle.[1b,10]

In the usual procedure the total energy is minimized through successive approximations each changing any of the described variables. Caution is necessary in energy minimization[11] since algorithms are not normally designed to move from one potential energy well to another.

Applications

The inclusion of parameters to describe the amide functionality in the molecular mechanics model has been used in the description of simple amides,[2] protein conformations,[4,13] protein folding,[14] protein solvent interactions,[5] protein-ligand interactions,[15] nucleic acid-protein interactions,[16] enzyme substrate interactions,[17] thermodynamic properties,[15] and vibrational analysis.[18]

Little calibration of amide force fields has been reported. An example of correlations to experimental data is shown in the calculations of properties of various crystals in Table I. The force field has been optimized to fit the heat of sublimation and dipole moments of the ten listed amides.[2a,2b] Though deviations exist, especially in formamide and glutaramide, the force field gives a reasonable correlation.

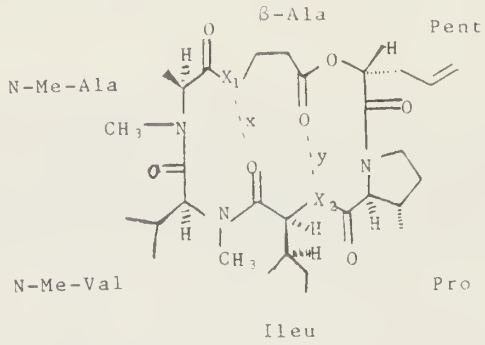
Table I

Experimental and calculated unit cell volume and hydrogen bond angles of amide crystals[2a,2b]

	unit cell volume Å		H···O=C angle in deg.		180-N−H···O angle in deg.	
crystal	expt	calc	expt	calc	expt	calc
oxamide	87.7	90.4	155	163	29	20
malonamide	950	949	144	147	29	29
succinamide	534	543	138	137	3	6
glutaramide	675	660	121	114	11	14
adipamide	354	359	151 146	162 147	28 35	17 34
urea	151	148	106	102	12	17
formamide	230	228	125	148	19	16
diketopiperazine	218	251	123	131	4	16
L,L−3,6−Dimethyl−2,5−piperazinedione	180	180	123	131	13	19
cyclopropanecarboxamide	934	930	136 115	128 115	19 10	22 6

Recently, molecular mechanics has been used to study conformations of Roseotoxin B (1a) and some related isoelectronic compounds.[19] (Fig.1)

Figure 1



	X_1	X_2
1a	NH	NH
1b	O	NH
1c	O	O

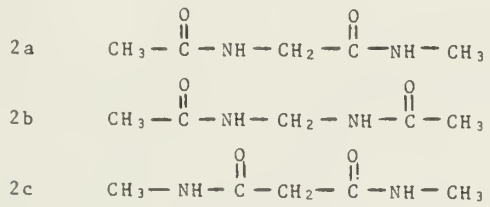
Roseotoxin B, a toxic metabolite produced by fungus found on moldy peanuts, has three distinct crystal structures.[20] Comparison of molecular mechanics optimized structures of Roseotoxin B with isoelectronic structures 1b and 1c is used to evaluate the importance of hydrogen bonds x and y to the primary molecular conformation. The representative data in Table II, comparing dihedral angles, show only slight tortional angle deviations. These data support the possibility that the intramolecular hydrogen bonds contribute only a small amount to the secondary structure in this conformation. No attempt was made to find a global energy minimum.[19]

Table II

Dihedral angles (in degrees) for molecular mechanics optimized structures[19]

angle	1a	1b	1c
Ile ϕ	-76	-72	-58
Ile ω	168	166	164
Val ϕ	-92	-98	-97
Val ψ	95	94	95
Ala ϕ	-138	-140	-141
Lactone	174	175	176
Pro ϕ	-81	-81	-75
Pro ψ	-17	-19	-30
Total $\phi/\psi/\omega$ deviation from 1a		3	7

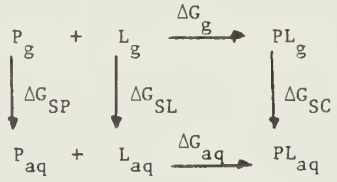
Another example from the study of retro-inverso peptides[21] compares the energy of rotation about ϕ, ψ, and corresponding angles of compounds 2a, b and c. These types of peptides may be active and less prone to biological degradation than normal peptides. Compound



2a yields two equivalent minimum conformations at ϕ, ψ = (-90, 80) = (90, -80). Compounds 2b and 2c both show two equivalent minimum conformations near angles (-80, -80) and (80, 80). Therefore, the conformational preferences of compounds 2b and 2c differ significantly from their peptide analog 2a. Incorporation of such moieties in a peptide chain can significantly alter conformational properties.[22]

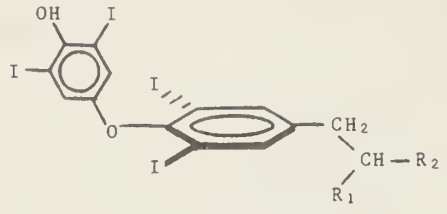
A final example involves the approximate calculation of the comparative free energy of complexation of the protein-ligand interactions of thyroxine analogs (Fig. 2) and prealbumin. Prealbumin is a protein which contains four subunits of 127 amino acids. Because of computer limitations it has been represented by 40 amino acids. The positions of the substrate, bound water, and the amino acids used to define the binding site are determined from X-ray and difference electron density maps studies. The thermodynamic cycle in Scheme I is used to estimate binding energies. P is the protein, L

Scheme I



the ligand. For one complex, $\Delta G_{aq} = \Delta G_g + \Delta G_{SC} - \Delta G_{SP} - \Delta G_{SL}$, and the difference in free energy between two complexes is $\Delta(\Delta G_{aq}) = \Delta(\Delta G_g) + \Delta(\Delta G_{SC}) - \Delta(\Delta G_{SP}) - \Delta(\Delta G_{SL})$. Assuming that the relative gaseous free energies of "gas phase" association can be approximated by relative internal energies $\Delta(\Delta G_g) \approx \Delta(\Delta E_g)$. The solvation energies of the protein and protein-ligand complex of different analogs are similar

Figure 2



	R_1	R_2
L—T_4	COO^-	NH_3^+
D—T_4	NH_3^+	COO^-
de—NH_3^+—T_4	H	COO^-
de—COO^-—T_4	NH_3^+	H

and thus $\Delta(\Delta G_{SP})$ and $\Delta(\Delta G_{SC})$ both equal 0. Therefore, $\Delta(\Delta G_{aq}) \approx \Delta(\Delta E_g) - \Delta(\Delta G_{SL})$. $\Delta(\Delta G_{SL})$ is estimated from comparison of glycine for L- and D-T_4, acetic acid for deamino-T_4 and methylamine for

Table III

Comparison of calculated and experimental difference in free energy of thyroxine analog - prealbumin complex

analog	$\Delta(\Delta G_{SL})$	$\Delta(\Delta E_g)$	$\Delta(\Delta G_{aq})$	$\Delta(\Delta G_{expt})$
L—T_4	-19.6	0.0	0.0	0.0
D—T_4	-19.6	2.4	2.4	2.01
de—NH_3^+—T_4	-9.8	4.7	-5.1	-0.67
de—COO^-—T_4	-9.8	13.9	4.1	3.45

* The best fit is where the dielectric constant is equal to the distance between moieties. $\Delta(\Delta G_{aq})$ has been adjusted so that L-T_4 = 0.

decarboxy-T_4. $\Delta(\Delta E_g)$ is obtained from force field calculations. The results in Table III illustrate at least qualitative agreement and are encouraging for future use of these types of calculations.[23]

In summary, force field calculations of amides have been shown to agree satisfactorily with experimental data by evidence from crystal data of ten amides. Applications of molecular mechanics have evaluated the importance of hydrogen bonding in the primary structure of Roseotoxin B, illustrated that retro-inverse peptides may be conformationally different from normal peptides, and qualitatively estimated the difference in the free energy of binding of thyroxine analogs to prealbumin. These examples illustrate the potential applications of force field calculations in organic chemistry.

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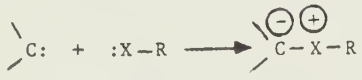
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STABLE YLIDES OF ELECTRONEGATIVE ELEMENTS

Reported by Charles F. Palmer, Jr. April 29, 1985

Ylide chemistry, as a branch of organic chemistry, has been a rapidly expanding field in the past fifteen years. Ylides can be defined as substances in which a carbanion is attached directly to a heteroatom carrying a high degree of positive charge.[1] Ylides can be formed in several different ways, but a method of much recent interest is the reaction of a carbene with a compound containing a heteroatom with an unshared pair of electrons.[2] (Scheme I) Such ylides are thought to be intermediates in many carbene reactions, and so with the isolation of stable ylides and the subsequent demonstration that the products of reactions of stable and unstable ylides are analogous, isolation of stable ylides has revealed much about the mechanism of carbene reactions. Much of the most recent work concerns ylides formed from reaction of carbenes with the more electronegative heteroatoms (N, O, halogen) since these have been the most difficult to isolate in stable form.

Scheme I



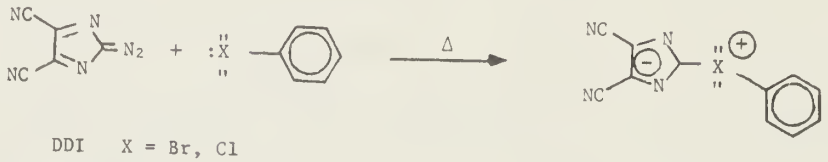
X = Group V, VI, VII element

Preparations of ammonium, pyridinium, and iminium ylides of nitrogen have been reviewed.[1] More recent work has been concerned with nitrilium[3,4,5] and carbonyl[6,7] ylides and their possible intermediacy in certain 1,3-dipolar cycloadditions. There has been some evidence for oxonium ylides as intermediates in reactions of alcohols and carbenes.[6f,8] Halonium, and especially iodonium, ylides have been investigated for a much longer time.[9,10]

In 1973 Sheppard and Webster published the synthesis of and the results of the reactions of diazodicyanoimidazole (DDI).[11] This carbene precursor was reacted thermally with aryl chlorides and aryl bromides to give the first stable isolable chloronium and bromonium ylides.[11,12] (Scheme II) Janulis and Arduengo have further developed the use of electron deficient five-membered rings to stabilize the carbanionic center of an ylide. The reactions of the carbene precursor, diazotetrakis(trifluoromethyl)cyclopentadiene (DTTC), have

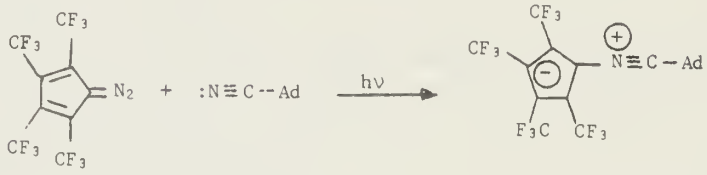
produced the first stable nitrilium and carbonyl ylides.[5a,6f] (Scheme III) This approach to synthesizing stable ylides of electronegative elements appears to be the most successful to date, and is continuing to be explored.

Scheme II

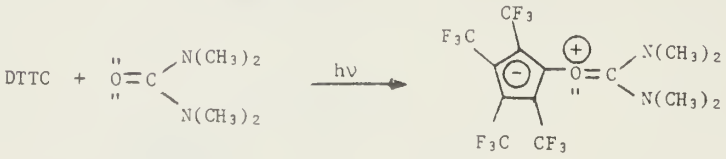


DDI X = Br, Cl

Scheme III



DTTC Ad = Adamantyl



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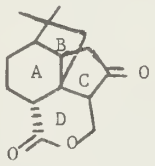
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TOTAL SYNTHESES OF QUADRONE

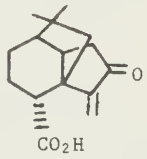
Reported by Gary A. Hite May 2, 1985

Isolated as a metabolite from the broth of the fungus Aspergillus terreus, quadrone **1** exhibits significant in vitro activity against KB human epidermoid carcinoma of the nasopharynx (ED_{50} 1.3 μg) and in vivo activity against P388 lymphocytic leukemia in mice.[1] The structure of this novel sesquiterpene was determined by single crystal X-ray diffraction; however, its absolute configuration was unknown until recent chiral non-racemic syntheses.[2] Its unusual tetracyclic structure includes five contiguous asymmetric centers, four of which are neopentyl. The fifth center is a quaternary carbon common to all four rings.

Recently, terrecyclic acid A **2**, known to be a synthetic precursor to quadrone, was isolated from another strain of A. terreus and shows antibiotic properties.[3] Due to its antitumor properties and its unique quadricyclic ring system, quadrone has been the focus of intense synthetic activity.[4]



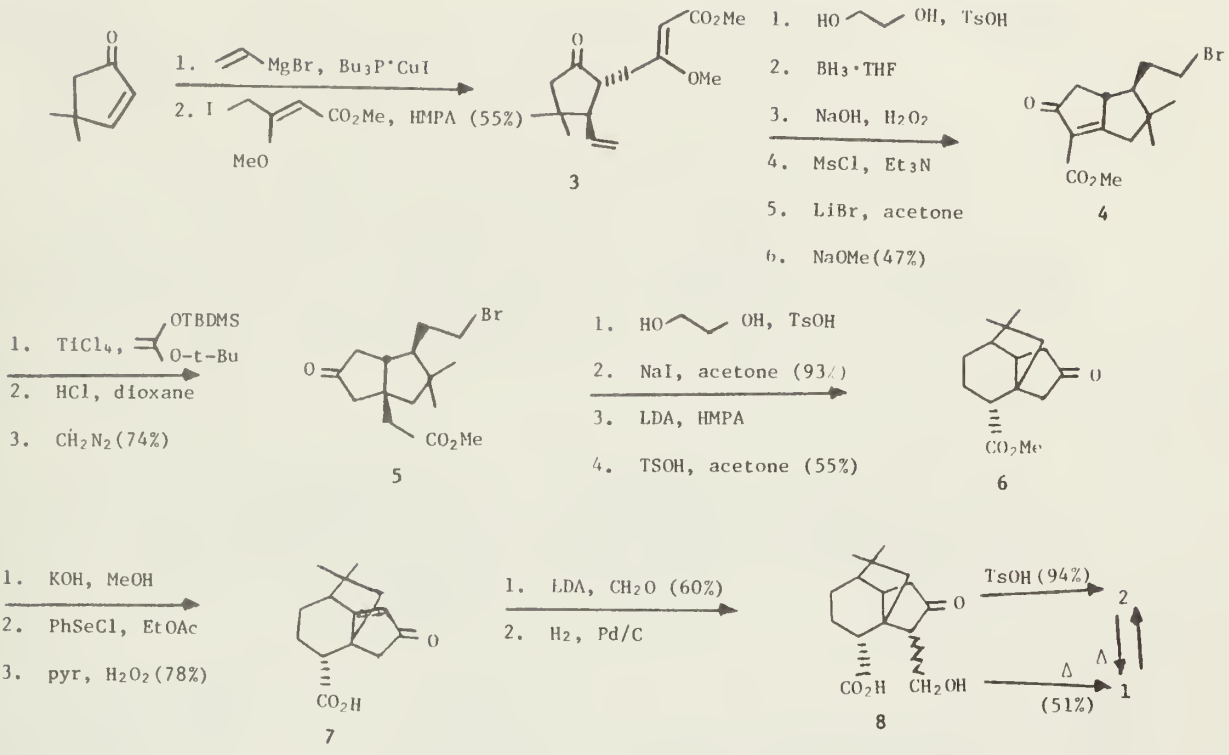
1



2

The first total synthesis of (±)-quadrone was accomplished by Danishefsky and co-workers,[4] while a similar strategy was being explored by Helquist[5] (Scheme I).[6] Conjugate addition of a vinyl group to 4,4-dimethylcyclopentenone followed by alkylation of the resulting enolate with 4-iodo-3-methoxycrotonate provided compound **3**. After ketalization of both ketones, the vinyl group was converted to a bromoethyl group with concurrent deprotection. Aldol cyclization followed by dehydration resulted in the key intermediate **4**. Compound **5** was then prepared using a Michael-type Mukaiyama addition[7] of a silyl ketene acetal, followed by decarboxylation, hydrolysis of the silylester, and esterification. After protection of the ketone and conversion to an iodide, the stage was set for intramolecular alkylation. Deprotonation was affected using LDA in THF at -78°C →

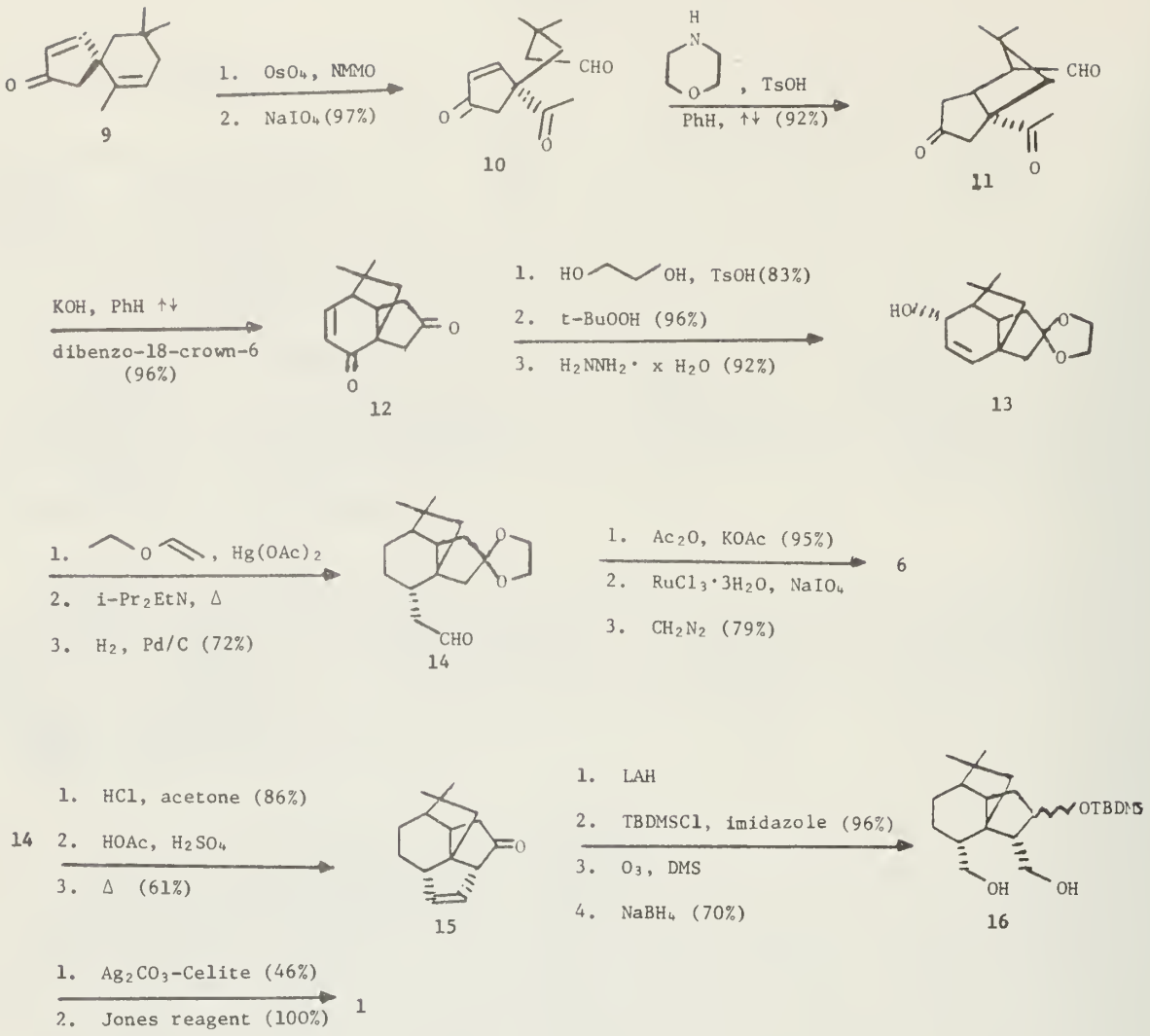
Scheme I[6]



-23°C. After addition of HMPA, the solution was warmed to room temperature and stirred for one hour. Standard workup followed by deketalization afforded the tricyclic keto ester **6**. Saponification and creation of unsaturation using phenylselenyl chloride created the enone acid **7** which could be hydroxymethylated regiospecifically. After hydrogenation, **8** was obtained which was easily converted into the methylene acid **2** (what is now known to be terrecyclic acid A). Pyrolysis of **2** produced an equilibrium mixture between **2** and **1** in a ratio of 1:4. Upon pyrolysis of **8**, quadrone **1** was produced in 51% yield. This 19-step synthesis achieved (±) quadrone in 3.1% overall yield according to the ring construction sequence B → C → A → D.

Burke et al[8] achieved a partially coincident total synthesis of (±) quadrone as well as a formal total synthesis. Starting with spiro[4.5]decadienone[9] **9** (Scheme II), readily available from dimedone, two-step oxidative cleavage (N-methylmorpholine N-oxide (NMMO), catalytic OsO_4[10] and then $NaIO_4$) produced **10**. Intramolecular

Scheme II



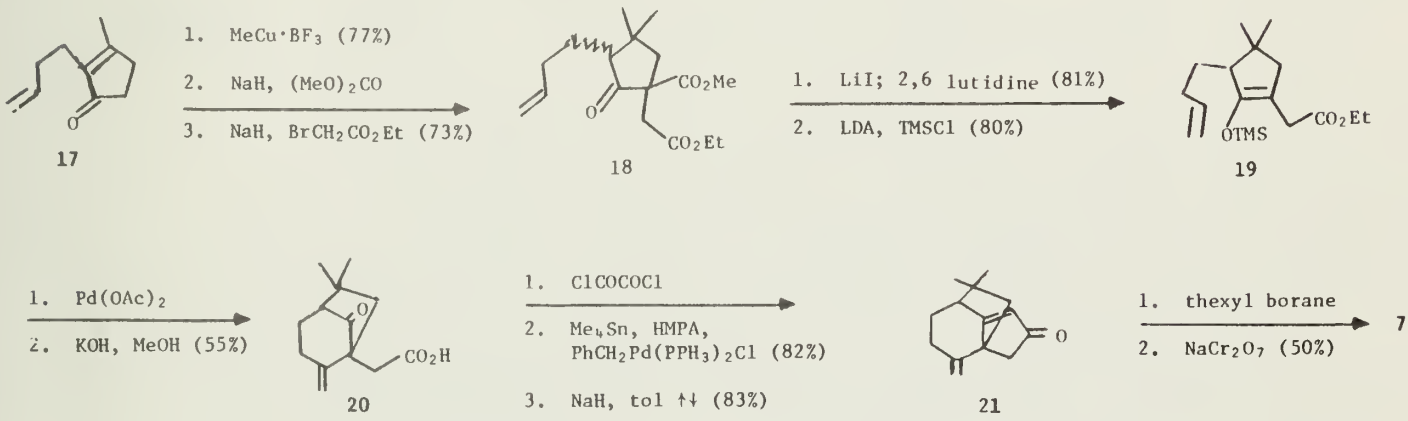
9 10 11 12 13 14 15 16

Michael addition produced the bicyclo[3.3.0]octane **11** which was cyclized under phase transfer conditions to give **12**. The tricyclic structure of quadrone was thus achieved very efficiently. Protection of the ketone, epoxidation from the α-face, and subsequent allylic transposition via the Wharton procedure[11] produced **13**. After treatment with ethylvinyl ether, a thermal aliphatic Claisen rearrangement (240°C, Hunig's base) and subsequent hydrogenation yielded **14**. Upon formation of the enol acetate, oxidative cleavage and deprotection were both achieved using $RuCl_3 \cdot nH_2O/NaIO_4$ in $CCl_4/CH_3CN/H_2O$.[12] Esterification produced the keto ester **6**, a Danishefsky synthesis intermediate, thus completing the formal synthesis. However, it was recognized that **14** already contained all the carbon atoms necessary to complete quadrone. Deprotection of the ketone followed by intramolecular aldol cyclization in glacial acetic acid produced a mixture of diastereomeric β-acetoxy ketones (4:1,

α-face acetoxy group predominating). Upon pyrolysis at 400°C a mixture of β-γ unsaturated ketone (61%) **15** and conjugated enone (33%) was produced. Reduction of the major product, followed by protection of the alcohol and ozonolysis with reductive workup produced the crystalline diol **16**. However, regioselective formation of the desired lactone could not be accomplished using a wide variety of oxidants. The 1:1 mixture produced by Fetizon's reagent[13] was easily separated and the correct isomer was deprotected and oxidized to yield (±) quadrone. This approach converted **9** → **1** in 19 steps in 6.2% overall yield according to the ring construction sequence C → B → A → D. Also notable in this approach was the fact that all carbon-carbon bond forming reactions were performed in an intramolecular fashion.

Kende and coworkers exploited a Pd(II)-mediated cycloalkenylation of a silyl enol ether in their formal total synthesis of quadrone (Scheme III).[14] Starting with known cyclopentenone[15] **17**, conjugate

Scheme III

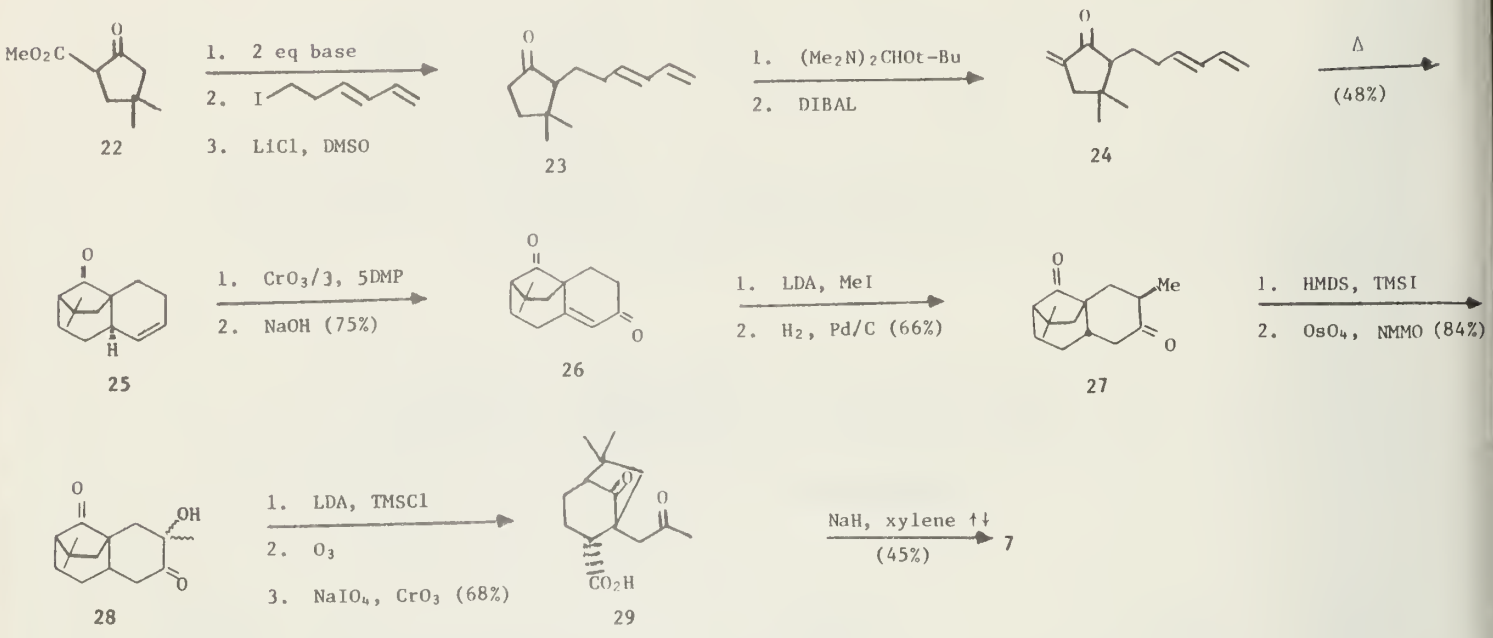


17 18 19 20 21

addition using $MeCu \cdot BF_3$[16] followed by carbomethoxylation and alkylation with ethyl bromoacetate produced the keto diester **18**. Nucleophilic decarboxylation yielded the γ-keto ester from which the required silyl enol ether **19** was formed under thermodynamic conditions. At room temperature using stoichiometric Pd(II) acetate an 8:1 mixture of isomeric bicyclic olefins was achieved (8 h) with the desired exocyclic olefin **20** predominating. Conversion[17] of the carboxylic acid into a methyl ketone allowed aldol cyclization to the tricyclic dienone **21**. Hydroboration and oxidation yielded the equatorial acid (18%) and the desired axial acid **7** in 50% yield thus completing the formal synthesis. This approach corresponds to 14 steps in 2.4% overall yield in the sequence B → A → C → D.

Schlessinger and coworkers utilized an intramolecular Diels-Alder reaction in their approach to quadrone (Scheme IV).[18] Vandewalle[19]

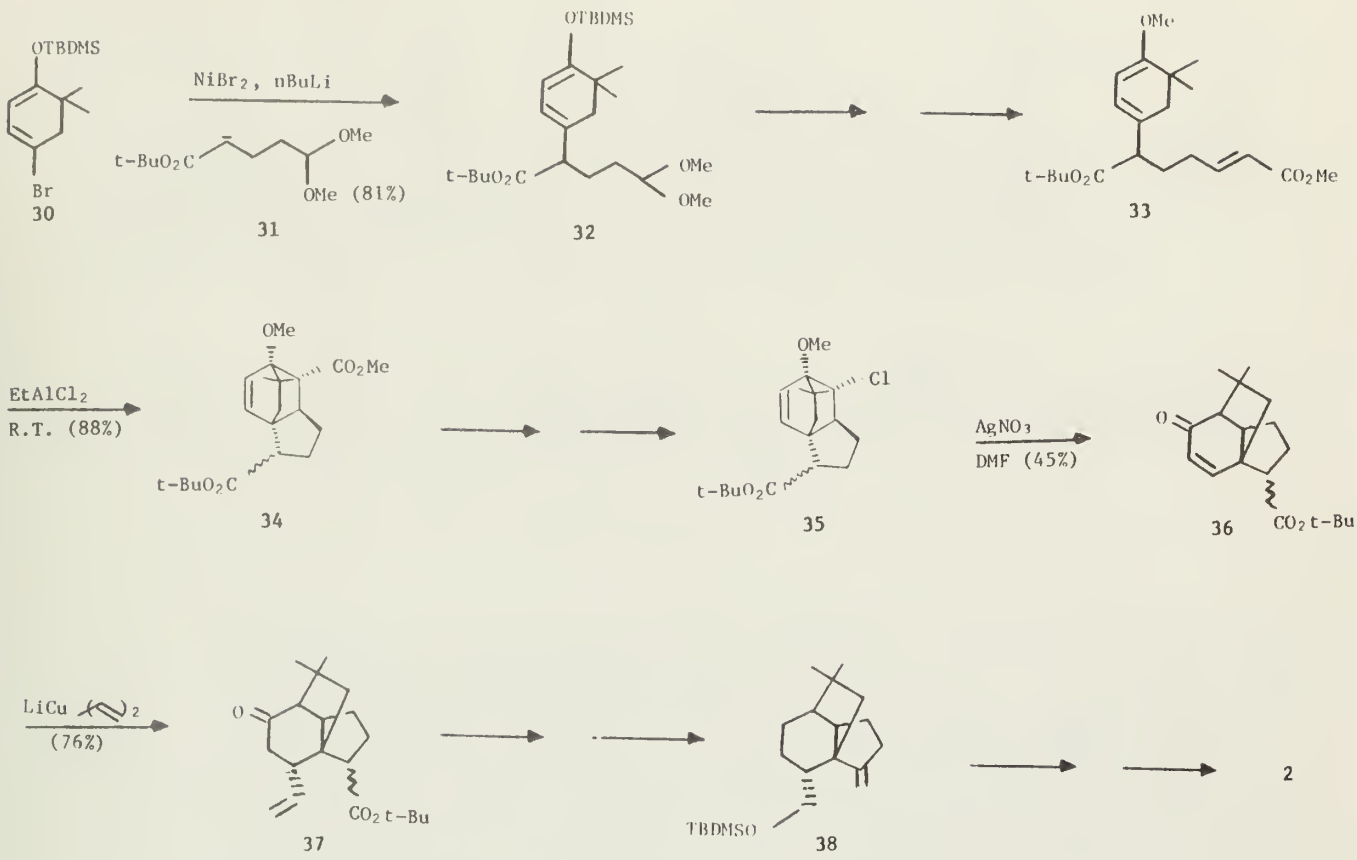
Scheme IV



used a similar strategy. Alkylation of the dianion of β-keto ester **22** with trans-1-iodo-3,5-hexadiene and subsequent decarboxylation produced **23**. Use of Brederick's reagent[20] followed by reduction yielded the exocyclic enone **24**. Cyclization in toluene/CH_3CN at 120°C produced the expected exo adduct **25** (based on steric considerations). This compound featuring a trans-decalin ring system was obtained in 48% yield from the starting material **22**. The enone **26** was achieved by allylic oxidation with CrO_3 and 3,5-dimethylpyrazole[21] (basic workup). Alkylation with iodomethane and hydrogenation yielded the required cis-decalin system **27**. Production of the more substituted silyl enol ether and subsequent oxidation with N-methylmorpholine N-oxide and catalytic OsO_4 resulted in the α-hydroxy ketone **28**. Trapping of the dianion with TMSCl and ozonolysis with oxidative degradation ($CrO_3/NaIO_4$) produced the diketo acid **29**. Aldol cyclization in refluxing xylene produced the known precursor **7** of quadrone in 13 steps and 6% overall yield in the ring sequence B → A → C.

Wender[23] and Wolanin have synthesized terrecyclic acid A also using a Diels-Alder reaction (Scheme V). Using their new γ-alkylation methodology, **32** was produced by coupling ester

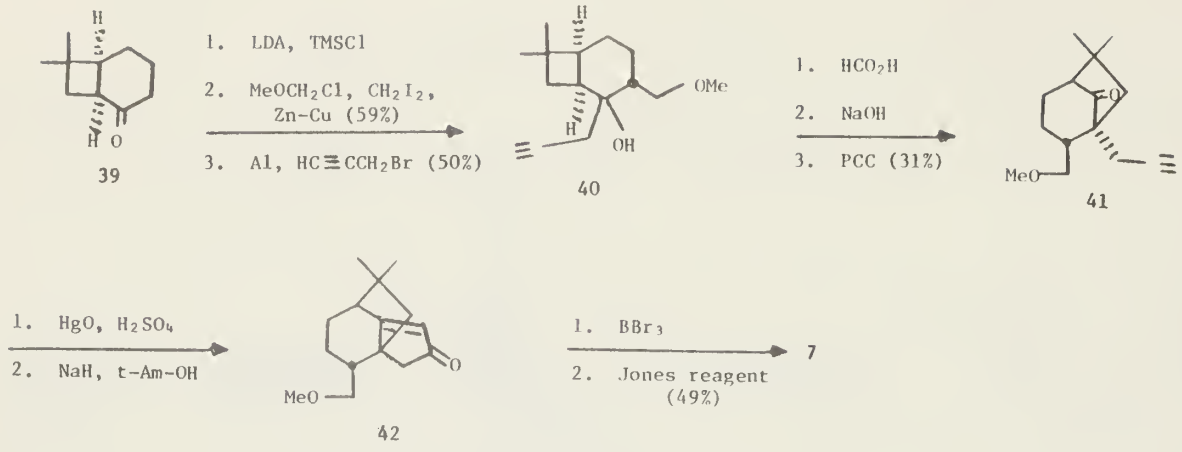
Scheme V



enolate **31** to bromo enol ether **30** using a $NiBr_2$/nBuLi reagent. Several steps later the triene **33** was cyclized at room temperature in one hour with ethylaluminum dichloride catalyst. This reaction yielded only endo-cycloadducts with the desired α-carbomethoxy stereoisomer **34** predominating (9:1). After conversion of the methyl ester to the chloride **35** ring expansion was affected with $AgNO_3$ to yield **36**. Conjugate addition with lithium divinyl cuprate added the last carbon atom necessary to complete the synthesis. Reductive fission of the ketone functionality in **37**, ozonolysis with reductive workup, protection of the alcohol, reduction of the ester and elimination afforded **38**. Then allylic oxidation, deprotection, and Jones oxidation produced terrecyclic acid A (**2**). This unpublished synthesis represents a unique annelation sequence, A → C → B.

Yoshii et al. employed a very concise synthetic approach (Scheme VI)[24] Starting with the photoadduct[25] 7,7-dimethyl-cis-bicyclo

Scheme VI

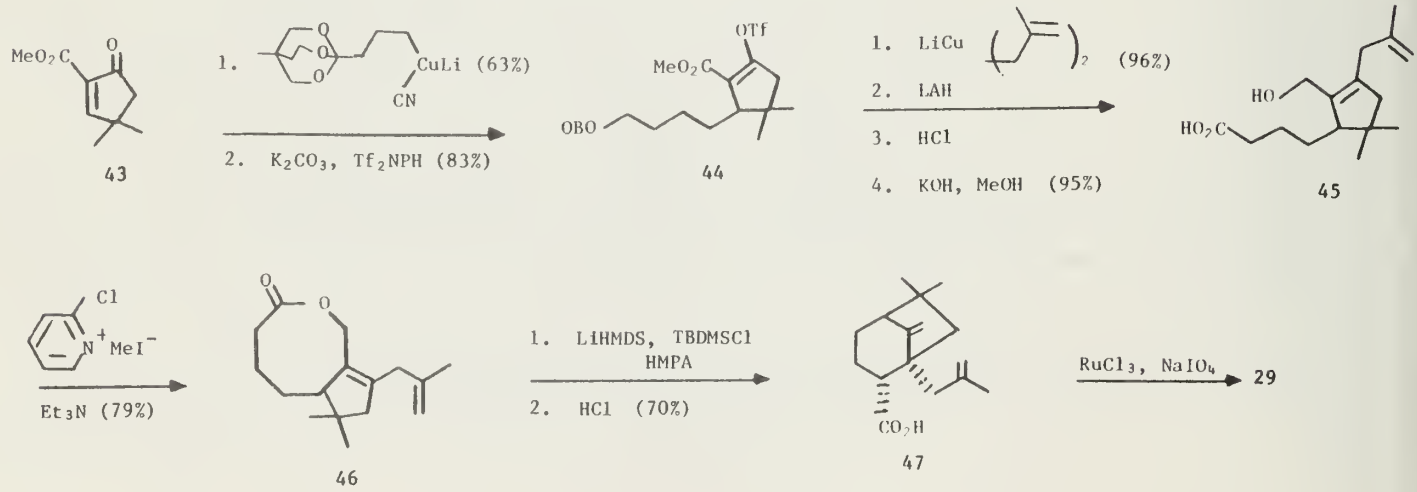


39 40 41 42

[4.2.0]octan-2-one **39**, a protected hydroxy methyl group was added by Shono's method.[26] By addition of propargylaluminum sesquibromide,[27] a latent acetonyl group, the key intermediate **40** was formed. Solvolytic rearrangement in formic acid gave a mixture of products containing the desired compound **41** in 31% yield after hydrolysis and oxidation. Hydrolysis of the triple bond afforded the diketone and aldol cyclization produced **42**, which was deprotected and oxidized to **7**, thus completing the formal total synthesis. This approach corresponds to a 12 step total synthesis in 2.6% overall yield by a unique A → B → C → D ring closure sequence.

Funk[28] and Abelman commenced their short synthesis (Scheme VII) with the conjugate addition of n-butyl-1-trioxa-bicyclo[2.2.2]octyl

Scheme VII

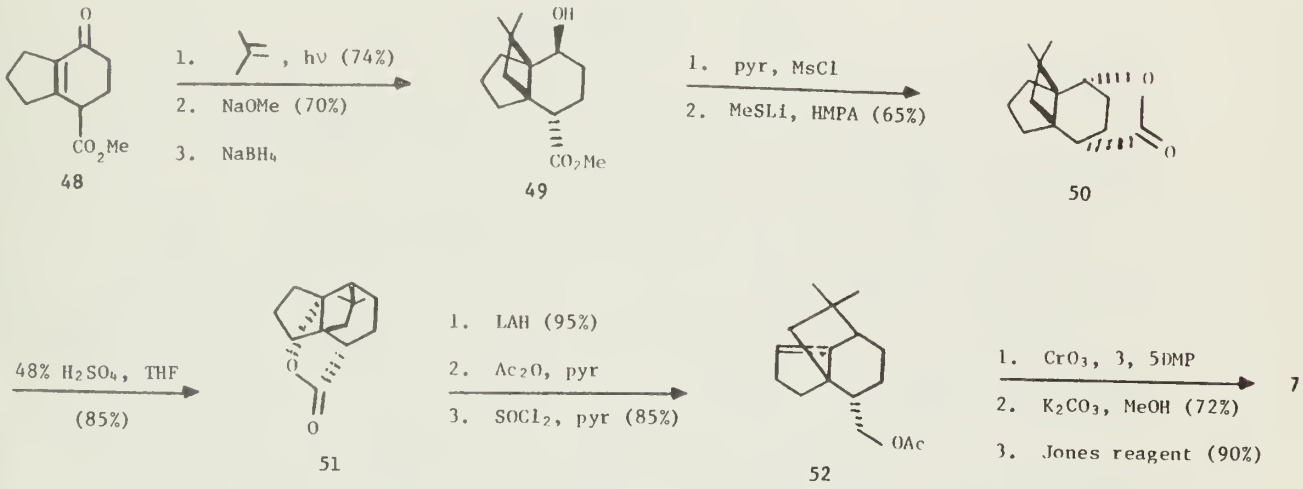


43 44 45 46 47

(OBO) ortho ester cyano cuprate[29] to enone ester **43**. After generation of the β-enol triflate[30] **44**, methallyl cuprate was added. Reduction of the ester, deprotection of the OBO ester and saponification produced substrate **45**. Lactonization was accomplished in refluxing CH_3CN (.005M) using Mukaiyama's salt.[31] Rearrangement of the silyl ketene acetal of **46** proceeded at or below room temperature to the silyl ester which was hydrolyzed to **47**. Upon oxidative cleavage with $RuCl_3 \cdot nH_2O/NaIO_4$,[12] diketone **29**, an intermediate in Schlessinger's synthesis, was produced. This approach corresponds to a 12 step total synthesis according to the sequence B → A → C → D.

Smith and coworkers have completed not only a formal total synthesis, but also a chiral non-racemic total synthesis (Scheme VIII).[2b] Photochemical cycloaddition of isobutylene to bicyclic

Scheme VIII



enone[32] **48** yielded a mixture of stereoisomeric esters with an anti:syn ratio of 1:2 (anti refers to the face opposite the cyclobutane); however, epimerization produced the anti-propellanone in a fivefold excess. Stereospecific reduction to **49** and mesylation, followed by nucleophilic displacement using methanethiolate in HMPA[33] yielded the key intermediate **50**. Acid-catalyzed rearrangement in 40% H_2SO_4/THF[34] at 50°C for one hour produced the new lactone **51**. Reduction, protection of the primary alcohol and elimination of the tertiary alcohol provided **52** possessing the carbocyclic skeleton of

quadrone. Allylic oxidation,[21] hydrolysis, and Jones oxidation provided the Danishefsky intermediate **7**, three steps away from quadrone. This strategy yielded (±) quadrone in 15 steps and 6.3% overall yield from **47**. For the non-racemic synthesis, alcohol **49** was reacted with (S)-(+)-O-acetylmandelic acid (DCC, DMAP, CH_2Cl_2)[35] to yield diastereomeric esters separable by HPLC in a 60:40 kinetic ratio (78%). After removal of the chiral auxiliary with NaOMe, **(+)-49** was converted to (+)-quadrone ($[\alpha]_D$+49.8°). Comparison with natural quadrone ($[\alpha]_D$-51.8°) indicated that the absolute configuration of natural quadrone was depicted by **1**. This result agreed with Isoe's conclusion[2a] from the synthesis of chiral non-racemic terrecyclic acid A from (+)-fenchone via a strategy almost identical to Danishefsky's approach.

It can therefore be seen that quadrone not only has biological activity but has served as a challenging goal for synthetic organic activity. Many additional model studies and skeleton syntheses further prove this observation.[36]

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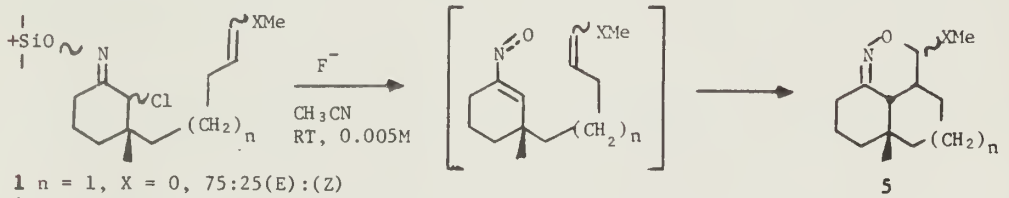
INTRAMOLECULAR [4 + 2] CYCLOADDITIONS OF TWO HETERODIENES; NITROSOALKENES AND UNSATURATED ALDEHYDES

Reported by Jeffrey A. Sternberg May 9, 1985

Since its discovery in 1928, the Diels-Alder reaction has been one of the most powerful tools in synthetic organic chemistry.[1] The simultaneous creation of four contiguous chiral centers with predictable relative stereochemical control has made the reaction extremely valuable in countless natural product syntheses.[2] Furthermore, intramolecular Diels-Alder reactions have been shown to exhibit greater regio- and stereochemical control, as well as higher reactivity, than their intermolecular counterparts.[3] In recent years, the use of heterodienes to construct various six-member ring heterocycles has attracted the attention of a number of researchers.[4] Two heterodienes of current interest are nitrosoalkenes[5] and (Z)-α,β-unsaturated aldehydes.[6]

Silyloximes **1-4** cyclize to the corresponding tricyclic dihydrooxazines **5-8** in moderate to good yield[7] (Scheme I). The success of the cycloaddition reaction displays a strong dependence on the ability of the dienophile to achieve secondary orbital overlap. Despite numerous attempts, the N-O bond in the cycloadducts could not be cleaved in order to expose the cis-fused perhydronaphthalene and perhydroindane ring systems.[8]

Scheme I

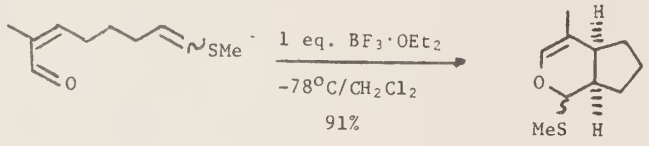


1 n = 1, X = O, 75:25(E):(Z)
2 n = 1, X = O, 50:50(E):(Z)
3 n = 1, X = S
4 n = 0, X = O

5
6
7
8

The use of (Z)-α,β-unsaturated aldehydes as heterodienes in intramolecular [4 + 2] cycloadditions has also been investigated.[6,8] (Z)-Enal **9** cyclizes stereoselectively affording the cis-fused cyclopentapyrans **10** in excellent yield (Scheme II).[8] Cyclization of the (E)-isomer of **9** under identical conditions produced all four possible stereoisomeric cycloadducts. Recently, this methodology has been applied to the synthesis of the iridoid monoterpene (+)-nepetalactone.[8]

Scheme II



9 **10**

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